ANNUAL REPORT OF PROGRAM ACTIVITIES

NATIONAL INSTITUTE OF MENTAL HEALTH

FISCAL YEAR 1973

PART I

U. S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE, NATIONAL INSTITUTES OF HEALTH

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ANNUAL REPORT

MENTAL HEALTH INTRAMURAL RESEARCH PROGRAM - Division of Clinical and Behavioral Research, and Division of Biological and Biochemical Research

NATIONAL INSTITUTE OF MENTAL HEALTH

July 1, 1972 - June 30, 1973

VOLUME I

Summary Statements

ANNUAL REPORT
MENTAL HEALTH INTRAMURAL RESEARCH PROGRAM -
Division of Clinical and Behavioral Research, and
Division of Biological and Biochemical Research
NATIONAL INSTITUTE OF MENTAL HEALTH

July 1, 1972 - June 30, 1973

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ANNUAL REPORT
of the
DIRECTOR, MENTAL HEALTH INTRAMURAL RESEARCH PROGRAM
NATIONAL INSTITUTE OF MENTAL HEALTH
July 1, 1972 - June 30, 1973

John C. Eberhart, Ph.D.

The single most significant event of the year for the NIMH Intramural Research Program is the announced return of the NIMH to the NIH as a part of a larger reorganization of HSMHA. I will say more about this later on. As one looks back on fiscal year 1973, it is necessary to note that the political or administrative context in which the year's research program has taken place is one of many months of reorganization in DHEW and in the rest of the Federal Government, much shifting of Cabinet officers and other officials as a consequence of the re-election of President Nixon, many periods of confusion from such shiftings, and much muddling through of periods when, as one senior official remarked to me, "There is now no effective governance in the Department." I am glad to say that throughout the year there was always effective governance in the NIMH. I hope there has been in the Intramural Program too, though the budgetary, personnel, travel, and other constraints under which we have operated (not much different from last year) have frequently made it difficult to conclude agreements and maintain commitments. They have also made it difficult to provide the support needed for a good deal of important research.

These notes are the second draft I have written for this annual report. The first, since discarded, dealt with the role of science in the Federal Government since the 1972 election, an unhappy account. One lives in this context of politics, good, bad, or indifferent, but in truth, the political events of the past 7 months have had little immediate and specific effect on this program; hence the discard. The potential long-range effects of these events are the source of my concern, and I hope that trends visible near the end of this year of the Watergate will make for happier reflections a year from now.

As this program has grown older the number of problems related to inflexibility of committed budgetary support has increased, and Dr. Robert A. Cohen's annual report as Director of the Division of Clinical and Behavioral Research is an important review of some of them. I commend it to all staff of the Intramural Program. Some of the issues he discusses will be on the agenda for discussion by Laboratory and Branch Chiefs at the "retreat" on June 12-13, 1973, at Cacapon Lodge, Berkeley Springs, West Virginia. This two-day meeting will be the second meeting of its kind. The first, a one-day affair in a Building 31 conference room on April 30, 1970, was a useful beginning but was too short to deal with certain major problems. It should not have taken us three years to organize a successor.

A major preoccupation of many staff members of this program during the past year has been work on the NIMH Research Task Force, which was outlined in

this report a year ago. Four of our scientists have been Task Force staff members--Drs. Donald Boomer, Patricia Goldman, William Pollin, and Philippe Cardon--spending most of their time in the effort. Some two dozen others have worked hard as members of subject matter committees, each of which is drafting a comprehensive report on the content of its discipline or problem area, achievements by the NIMH so far, problems or research directions that now appear important for future pursuit, and recommendations for organization or administration of research programs. The Coordinating Committee of the Task Force, consisting of committee chairmen, research-involved Division Directors, and certain others, has met periodically to hear progress reports from the committees and from Task Force staff, and to debate such matters as research priorities, the criterion of relevance, "balance" in research programs, etc. The final report is now expected to be ready in September, in time for review by the ad hoc committee of outside reviewers.

In the midst of these political, organizational, and institutional matters, the research programs have continued quite successfully, as the following summaries by the Laboratory Chiefs make clear. A number of prizes and other awards were again made to members of the staff. Dr. Floyd E. Bloom was given the Arthur S. Flemming Award as one of the 10 outstanding young men in the Federal Government, and was chosen by a distinguished group of outside scientists as the first Mathilde Solowey Lecturer at the NIH. The Psychopharmacological Award of the American Psychological Association was given this year to Drs. Richard Wyatt, Marc Galanter, and Richard Stillman for research reported in their paper on "State Dependency Learning While Taking Marihuana." Dr. Herbert Weingarten of the University of Maryland shared in the award. Dr. Richard L. Veech received the first Bly Foundation Memorial Award of a plaque and a $500 honorarium for "his major contributions to understanding the reactions of brain and liver tissues to alcohol." Dr. Robert Post, an NIMH Special Fellow working in the Laboratory of Clinical Science, received the A.E. Bennett award from the American Society of Biological Psychiatry. Dr. Julius Axelrod received another honorary degree; this one the Sc.D. from the City University of New York; and Dr. Erminio Costa was elected as the first Emeritus Foreign Member of the Indian Pharmacological Society in Jaipur, India, December 1972.

In addition to awards for members of the scientific staff, it is a pleasure to report that the Department's Superior Service Award, given by the Administrator of the Health Services and Mental Health Administration, this year honored three members of our administrative and services staff. They were: Mrs. Anne Gibson, Assistant to the Administrative Officer, Division of Special Mental Health Research, who has done an outstanding job since she joined the Intramural Research Program staff in 1957; Mr. Leo Leitner, Supervisory Electronics Technician in the Section on Technical Development, whose good judgment, managerial skill, and technical virtuosity have played an important role in the achievements of the Section on Technical Development; and Miss Alice Muth, Assistant to the Administrative Officer, IR, whose administrative wisdom, devotion, and extraordinary capacity for getting everything right have had a major impact on the whole Intramural Program. I would like to add that Miss Muth, despite her youth, is the senior member of the NIMH staff in length of service at NIMH, having come to work for the predecessor Division of Mental Hygiene in 1946.

I mentioned above that the NIMH was returning to the NIH. For the record I would like to add a few details. A decision was made about May 1 by the Office of the Secretary that the Health Services and Mental Health Administration would be reorganized, to produce the following: (1) HSMHA would be abolished; (2) the CDC (Center for Disease Control) would be continued as an independent health agency; (3) certain HSMHA functions would be regrouped as a new health agency, the Health Services Administration (HSA); (4) certain other HSMHA functions, plus the Bureau of Health Manpower from the NIH, would be combined into another new health agency, the Health Resources Administration (HRA); and (5) the NIMH, intact as now constituted, would be transferred to the NIH. (Further study of the internal structure of the NIMH is continuing.) The reorganization is expected to be completed by July 1, 1973. For the present, no physical moves are planned for either the Bureau now housed at NIH, or for the NIMH staff now in the Parklawn Building.

For the Intramural staff the reuniting of NIMH and NIH is a cause for rejoicing, and I venture to hope that the change in affiliation will please the rest of the NIMH as well. We in Intramural have operated through two chains of command for 7 years: through NIMH-HSMHA, where we formally belonged, and through NIH, which had joint administrative responsibility for us. We will now return to the normal status of having just one set of bosses. Someone has said that the move will bring mental health to the NIH. Perhaps there is a sense in which, in return, science can more effectively be brought to mental health.

The fall meeting of the NIMH Board of Scientific Counselors was held at the NIH Animal Center in Poolesville to review the current program and future research plans of the Laboratory of Brain Evolution and Behavior. The programs of Drs. MacLean, Stanley, Calhoun, and their junior colleagues were included. The dates were October 27-28, 1972. The Board was short-handed, but all four members were present: Drs. Eugene Bliss, Walle Nauta, Richard Solomon, and Robert Stubblefield. On March 30-31, 1973, the Board met in Building 36 to review the work of the Laboratory of Socio-environmental Studies, less the child development research of Dr. Yarrow and colleagues. Included in the review were the programs of Drs. Kohn, Rosenberg, Pearlin, Schooler, and McQueen. All four members of the Board were present, and because there were no sociologists on the Board we invited two sociology consultants to sit with the Board for this review. Dr. William Sewell, Professor of Sociology at the University of Wisconsin, and Dr. Rose Coser, Professor of Sociology at the State University of New York, Stony Brook, accepted our invitation and performed a major service. They were so useful that we perhaps should supplement the regular Board with a specialist or two at many future reviews.

Dr. Richard L. Solomon has served as Chairman of the Board for the past two years, and it is with regret that I note the expiration of his term on June 30, 1973. He has been a solid and consistently critical and helpful member, and a fine Chairman, and I want to thank him and the other members for their contribution to making this a good program.

Only one member of our staff was on a foreign work assignment this year. Dr. Frederick Snyder, Chief of the Laboratory of Clinical Psychobiology, was

in Nairobi, Kenya, carrying out research on the sleeping-waking behavior of some of East Africa's exotic mammals by means of telemetry. He also held a faculty appointment in the Department of Psychiatry of the University of Kenya.

This year has seen the departure of four of our senior scientists and the replacement of two of our four principal administrative officers; coming up soon, on June 30, is the scheduled departure of two other major figures.

Leaving during this year were Dr. Walter Freygang, for many years a member of the staff of the Laboratory of Neurophysiology, who retired from the Commissioned Corps in October 1972; Dr. David Carpenter, also from the Neurophysiology Laboratory; Dr. Winfield Scott, psychologist in the Adult Psychiatry Branch; and Dr. Roger McDonald, Chief of the Clinical Psychopharmacology Laboratory in the Division of Special Mental Health Research. Drs. Freygang and McDonald have spent most of their professional careers in the NIMH Intramural Research Program and both have made major scientific contributions. Drs. Scott and Carpenter are younger, but both have done excellent work in their specialties. We shall miss them all.

We are very pleased that one of our former staff members will be returning to Intramural, probably this September. Dr. William E. Bunney, formerly Chief of the Psychiatry Section in the Laboratory of Clinical Science, and before that a member of the Adult Psychiatry Branch, has spent the past 21 months serving as Director of the Division of Narcotic Addiction and Drug Abuse in the NIMH. He has accepted our invitation to become Chief of the Adult Psychiatry Branch, succeeding Dr. Lyman Wynne. We are looking forward to his return.

Both John Land and John Proctor, Administrative Officers for the Division of Clinical and Behavioral Research and the Division of Special Mental Health Research respectively, left during the year for other opportunities. We are all grateful to them for their untiring efforts to manage what are often unmanageable operations. Mr. Land was succeeded by Mr. Patrick Talmon and Mr. Proctor by Mrs. Margaret Ouellette. We welcome them both and assure them of our cooperation and appreciation.

On June 30, we will lose two major staff members. Mr. James Bryan, Chief of the Section on Technical Development, is resigning to go into private consulting in Pennsylvania. He has wisely and skillfully managed this engineering enterprise and has guided me and others through the baffling byways of computers, hardware and software, on-line and off, to everyone's gain. We wish him well in his new career, and are glad that he will be spending some time with us next year as a consultant.

Finally, I regret to report that Dr. Gian Carlo Salmoiraghi, Director of the Division of Special Mental Health Research, and a member of our staff since 1957, will be resigning his post on June 30, 1973, to become Associate Commissioner for Research, New York State Department of Mental Hygiene at Albany. In an often difficult situation, Dr. Salmoiraghi has been a strong and effective administrator, and an excellent picker of talented young scientists. The high quality of his Division's program is

testimony to the quality of the man. He is a hard man to spare, and we shall miss him very much.

We are fortunate that Dr. Floyd E. Bloom, Chief of the Laboratory of Neuropharmacology in the DSMHR, has agreed to serve as Acting Director of DSMHR when Dr. Salmoiraghi leaves. Dr. Bloom is already a distinguished scientist at an early age, and has been an effective Laboratory Chief.

I regret to report the death of Dr. Wade H. Marshall on November 14, 1972. Dr. Marshall retired as Chief of the Laboratory of Neurophysiology on July 10, 1970, and had continued writing after his retirement. At the wish of the present members of the Neurophysiology Laboratory the library adjacent to Dr. Marshall's former office has been dedicated as the Wade H. Marshall Library, and has been marked by a brass plaque.

Annual Report of the
Director, Division of Clinical and Behavioral Research
National Institute of Mental Health

July 1, 1972 - June 30, 1973

Robert A. Cohen, M.D., Ph.D.

From the point of view of program administration this has been a difficult year. The increasing costs of carrying on research have been coupled with restrictions on budget, hiring and even on promotion. We have had to face squarely the issue of whether all should suffer equal constraint or whether we should give maximum available support to those programs which are somewhat more likely to make significant early progress. In past years we had chosen the former alternative for several reasons. First, we regard this as primarily a basic rather than an applied research program. A central goal has been to make contributions to a more powerful theory of behavior and to an understanding of the psychosocial and biological processes which shape and mediate it. We had established, therefore, a multidisciplinary program because the formulation of such theory depends on knowledge which must be provided by all the relevant disciplines and could not come from one or two alone. We recognized and accepted the fact that it would not be likely that progress would be made with equal rapidity on all fronts. Even were all other things equal, the psychosocial sciences would encounter relatively greater difficulties in this institution which was specifically designed, constructed and organized to give maximal support to the biomedical sciences.

Partly as corollary to this early decision and partly influenced by the unalterable given of a personnel system which with some exceptions bestows upon Federal employees almost instant life-time tenure, we assumed long-term obligations to our scientific staff. While this policy posed obvious problems from a long-term institutional point of view, it had the advantage of permitting commitment to difficult problems which, if solved, would yield truly significant information. Investigators were not forced to select "sure bets" which are scientifically popular and impressive enough to bring favorable notice but not necessarily contributory to our ultimate goal. In the early days of the program this commitment did not pose a major problem. Great care had been exercised in staff selection, and all promotion recommendations were subjected to intensive scrutiny by the group of Scientific Directors of all the NIH Institutes. Internal requirements at every professional level exceeded Civil Service standards, and emphasized excellence rather than adequacy. Many outstanding investigators were attracted to the Clinical Center by the unexcelled facilities and by the offer of long-term support for problems to be freely chosen by the scientist himself. Our early concern was with our ability to retain the outstanding individuals who had inaugurated our research activities. But then the quite unanticipated vast increase in Federal support for biomedical research

provided universities with the means to augment their own research activities, and they naturally attempted to recruit leading figures in the field to direct their expanding programs. It took five years to assemble the first group of six laboratory chiefs in what is now the Division of Clinical and Behavioral Research. In two years, four of them left to assume professorships and departmental chairmanships at leading universities. And when one of them returned to the Clinical Center, his place was taken by one of the two who had remained.

In view of the intense competition with the universities for every notable research leader, and their movement from one institution to another as described so vividly in "The Academic Marketplace," we decided to select promising younger individuals and give them the support not then so readily available to them elsewhere which might enable them to carry out at the Clinical Center research of the highest quality. Since we believed that the way in which research is pursued is a highly idiosyncratic matter, we endeavored to give each of them considerable freedom in the structuring of his own program. Looking back, it seems to me that this was the golden age of this Division. The investigators made us look like wise administrators indeed since each of the laboratories received from its peers in the professional community an unusually large number of highly regarded international and national awards for scientific achievement. In part, our appointments had been wise since the investigators proved to be gifted scientists. But it was also true that our situation at that time was extraordinarily favorable, and made possible a unique responsiveness to the investigators' needs. A visitor described the Clinical Center as a place suspended somewhere between Paradise and Earth, and in many ways this was true. Each member of the staff received support which, if not always optimal, was at least generous. The program director had a sufficient reserve of money, positions and space so that developing needs could usually be met without withdrawing support from someone else. It was to be expected, of course, that not all the research achievements would be equally impressive, that some would stimulate a veritable explosion of work in new areas while others would sink quietly and at least temporarily unnoticed in the ever-increasing sea of scientific knowledge. This, after all, is the fate of most investigative work. We believed that this was not cause for concern but was, rather, part of the cost of research achievement. One did, of course, give thorough consideration to each new research proposal and to adequacy of the methodology to be employed in carrying it out. And, to use Adolf Meyer's phrase, one did not attempt to unscrew the inscrutable. But we had the enviable, perhaps the necessary luxury of being able to fail without feeling that thereby we would lose support for subsequent studies. For a time we took the somewhat Utopian position that each investigator was his own severest critic. It seemed to us that the situation in American science was such that when an investigator found that he was not making a significant contribution in this research factory, he would move of his own accord to a setting which gave him a better scope for his particular range of interests and talents.

Institutions, like individuals, go through developmental phases, and the experiences in each phase determine to a degree what happens in the next.

Would stricter controls in this early period have increased our research productivity? Would we have benefited from a more formal review of each research proposal, a more restrictive consideration of its promise and feasibility? If an investigator's achievements proved to be at a journeyman's level, should we have progressively restricted his resources even to the point of asking him to leave the program? Should we have supported only those whose work proved outstanding? The answers to these questions are arguable. I feel certain that we might have cut off some research which proved to be indifferent, and equally certain that we would have cut off other studies which took some time before they ultimately proved significant and important. But whatever may have been true in those relatively happy days, a continuation of the early policies no longer seems feasible in our present or immediately-foreseeable situation.

First and foremost is the marked decrease in the frequency of faculty movement between universities. Where once we searched far and wide to find investigators who would be willing to come to NIMH and resigned ourselves to the likelihood that their stay would be brief, now universities no longer seduce every investigator who moves and breathes. As they have had to cut back their science departments and the numbers of graduate students, our Federal Civil Service positions become relatively more attractive.

The size and support of the Intramural Research Program were also reduced. Our first response was to cut back the basic laboratories so that we might maintain the level of patient care on the clinical wards; then we were forced to reduce the clinical services, and now no one gets the support that everyone once received. The lack of movement out has meant that for some groups there has been no movement in, and we have no place now for the promising young investigators who fifteen years ago laid the foundations for the high esteem we still enjoy. And if by any chance we could bring one such person to the group, we could not possibly provide the resources which were indispensable to his predecessor's achievements. We still have a large budget and a large number of positions; we could still carry out many investigations each of which could be generously supported. But the cold, cruel fact is that we cannot give generous support to all the investigators and all the studies we are currently supporting. We cannot increase the resources for any individual without taking them away from another. Does this mean that the program as a whole will be less productive? Is the former level of support only conducive rather than essential for the most creative work? If it is essential, can we long afford to carry on without a change being forced upon us from the outside?

It is not hyperbole to say that our situation contains the seeds of a crisis. One measure of an institution's strength is its ability to survive crises. Since each of us sees this situation from his individual perspective, it is unlikely that we shall enjoy the luxury of achieving a consensus on how best to cope with it. An example of the difficulty was our decision to offer the post of Chief of the Adult Psychiatry

Branch to Dr. William E. Bunney, Jr. I am pleased to report his acceptance of the offer; he will assume his new duties not later than September, 1973 when he will return full-time to the Intramural Program after serving for almost two years as Director, Division of Narcotic Addiction and Drug Abuse. This decision to augment an unusually productive psychobiological research program at the expense of psychosocial studies was not unanimously endorsed by the laboratory chiefs in this Division or by the members of the Branch. The laboratory chiefs, meeting as a committee, had discussed the issue for almost two years, had considered a number of alternatives which included even the possibility of major reorganization of the Division's program; they remained divided on every proposal which was seriously considered. Those who opposed the final decision saw in it a turning away from our original goal of stressing the multidisciplinary nature of mental health research as well as from our early practice of almost indefinite commitment to competent scientists as long as they maintained an interest in their particular areas of research. It was feared that this change of direction inaugurated after the resignation of a branch chief would make the entire staff feel insecure, would alter the atmosphere we had labored so hard to achieve and which was deemed essential to the conduct of the best research.

Obviously, in making this decision we were not unaware of the merit of these considerations. In fact, one reason for the long delay in naming a Branch Chief after Dr. Lyman Wynne's resignation was recognition that a change in direction of the Branch program had the most serious implications for the Division and extramurally as well. It might be, and indeed already has been construed by some as an official National Institute of Mental Health decision to discontinue support for an important area of behavioral research. In the end, we concluded that the program proposed by Dr. Bunney would make the best use of the facilities available. He and his colleagues, Dr. Frederick Goodwin and Dr. Dennis Murphy, had already distinguished themselves as one of the most powerful and productive groups in psychobiology. In addition to its own inherent strength, this group utilizes to the full the unique resources of the Clinical Center and derives added support from its interactions with the biomedical laboratories in our own and other NIH Institutes. It has established itself as an outstanding training center for young scientists, and continues to attract superior research and clinical associates. While the more psychosocially oriented studies which have been carried out in the Adult Psychiatry Branch have also been of excellent quality, the benefits they derive from their presence in the Clinical Center are predominantly the non-specific ones afforded all of our research groups. Many of the principal interactions are with individuals and programs outside the Clinical Center. The setting here is adequate rather than ideal for the work. The restrictions imposed upon the program as a whole by the steady erosion of Clinical Center services weigh more heavily upon this program.

The decision to change research direction in the absence of general consensus is a matter of concern to the scientific staff. This is the first occasion in the history of this Division on which it has occurred.

We are engaged in discussions with the Laboratory and Branch Chiefs and with a committee from the Assembly of Scientists with the goal of defining a means of maintaining what we regard as an absolutely essential degree of program flexibility while still affording the investigators who may in future be affected the respect and consideration they deserve.

ANNUAL REPORT OF THE ADULT PSYCHIATRY BRANCH
National Institute of Mental Health
July 1, 1972 - June 30, 1973

David Reiss, M.D., Acting Chief

During this past year the work of the Branch was deeply marked by the uncertainty about the future of many of its programs and the ultimate decision to substantially alter the major direction of its efforts. Uncertainty and change always require painful readjustments. However, the Branch faced three additional problems that are not typical components of program change. These additional problems exacted a very heavy toll on staff and work. They are reviewed here in a constructive spirit: this description may help to ease the difficulties of program transitions in the future.

The first special problem was the length of time taken to reach a decision on the future of the Branch. Dr. Wynne gave three month's notice of his resignation as Branch Chief during April of 1971. Thus, as this report is written, 23 months have elapsed with neither definite word as to who the new chief will be nor precisely what research work he will permit. Unfortunately, during this period, the Branch has been repeatedly told that notice of its future would soon be given. Thus, long-range planning of any kind has been virtually paralyzed. Under these circumstances, it goes without saying that starting new projects or hiring of permanent scientific staff, to fill vacancies, has been impossible. Especially unfortunate, however, has been the steady erosion of long-standing and productive relationships with other institutions. In order to be nurtured, these collaborative relationships required long-term commitments on both sides: the collaborators needed to be assured that Branch investigators could be counted on for the duration of shared projects and the investigators needed to insist that their collaborators commit the necessary resources and personnel to collaborative work. In the hopes that their collaborative work with these institutions might ultimately be supported, the Branch's investigators sought to maintain their relationships with these institutions, in various states of suspension, by periodic appeals for their patience and forebearance. However, as time went on this pattern produced strain and tension on both sides of the relationships. The decay of these collaborations has caused curtailment or elimination of several projects and has put the Intramural Program into something of a bad light.

The second special problem has been the lack of an adequate, clear-cut interim work arrangement for support of on-going work during the lengthy decision-making period. Dr. Reiss was appointed Acting Chief for a period of one year on July 1, 1972, with implicit assurances that program support would continue through that period. However, no assurances were given beyond that point. Thus, staff members were faced with curtailing projects that would extend beyond that time or gambling on continued support after July 1, 1973. Since most significant projects in the Branch would not be completed by that date, this was a major dilemma. The problem was exacerbated by the need to replace departing staff and to make arrangements with

incoming clinical associates to whom commitments had been made years before. The experience of the past year clearly justified the view held by most Branch investigators at the outset: an interim period of two years is essential for meaningful support of the kind of long-term work characteristic of the Branch.

A third special problem arose, after the announcement in early January of 1973, that the direction of work in the Branch would be shifted to concentrate more heavily on biologic phenomena and that a scientist, with a background appropriate to this new emphasis, had been offered the position of Branch Chief. At this point several senior scientists, whose interests lie in different directions, reasonably concluded that they could no longer expect long-term support for their work. On their behalf, the Acting Chief made a number of unsuccessful attempts to clarify what support would be available for tapering-off this work. Three issues were paramount: conscientious planning for termination of clinical programs, efficient termination of on-going research and a reasonable consideration for the careers of scientific and supporting staff. Although a verbal arrangement for a minimum of 17 months for tapering off projects was offered to the Branch later in January, several attempts to clarify the specific implications of this arrangement have been unproductive. This lack of clarity has imposed the greatest stress of all on people and projects. Staff morale, already challenged by nearly two years of uncertainty, was maintained only by the most strenuous efforts. Several senior staff members have had to conclude that their best course was to leave the program as soon as possible. Many promising projects have been stopped abruptly in mid-course.

Of all the negative effects following from these additional and probably unnecessary problems, this stress on people's lives must be singled out for special emphasis. Supporting staff have been forced to work in a climate of tension and uncertainty for month after month. High levels of patient care could only be maintained by extraordinary efforts of our clinical staff. Finally, the senior scientific staff have been dismayed by the failure to give them any meaningful short or long-term assurances following the decision to change the emphasis of the program. One after another these men, whose tenure in the program ranges from 6 to 15 years, have sought to make meaningful arrangements to continue their work over a brief period of time or to wind-down their projects with the least injury to work in progress or to their careers. In several cases, failing to obtain <u>any</u> clarification whatsoever, some of them have had to conclude that their only course was to leave the program as soon as possible no matter what the cost. As other institutions have come to wonder about the reliability of commitments made by the Intramural Program so too have scientists within the program itself.

It is important to emphasize that, despite these major obstacles, productive work continued in all sections of the Branch this year. However, a careful reading of the section summaries and individual project reports will reveal this pattern: the only investigators who escaped unscathed were those holding appointments in other branches and whose own careers in the program were therefore, not immediately threatened.

SECTION ON FAMILY STUDIES

Helm Stierlin, M. D.

Dr. Stierlin's longitudinal project on separation in adolescence, carried out in cooperation with Drs. Robert Savard, Margaret T. Singer, and others, has reached its final phase. Altogether, 43 index patients with their families have passed through this project. Nineteen additional families were seen in screening sessions only. Twenty adolescents and their families were seen on an outpatient, and 23 on an inpatient basis. Thirty-two families were followed-up with systematic interviews; three more are still to be seen, while seven families out of a total of 43 either refused to be followed-up or moved out of the Washington, D.C. area. However, also on most of these families valuable, though unsystematic, information could be obtained. The adolescents - high risks for schizophrenia and other serious psychopathology- were referred to as "underachievers" and, together with their families were seen in conjoint family therapy for a minimum of three months and a maximum of two years. During the last three years most of these adolescents were hospitalized on 3-West while their families were seen in outpatient family and couple therapy. In addition to participating in therapy, the family members were individually interviewed and comprehensively tested. Detailed predictions were made after the initial screening session and at the end of the therapy. With the follow-up nearly completed, these predictions are now being checked out.

Even though the systematic analysis of data from this project remains largely to be done, many valuable findings have already accrued. Most importantly, the project has yielded a conceptual framework which allows a more detailed, as well as more comprehensive, understanding of the adolescent separation processes than seemed possible before. Crucial to this conceptual framework is the concept of transactional modes which include the modes of binding, delegating, and expelling. These modes have been delineated and clinically elucidated in about half a dozen papers, either published or accepted for publication. Specifically, they have been utilized to understand the phenomenology and dynamics of schizophrenic breakdowns in adolescence, to distinguish between different types of runaways, and other adolescent delinquents, and to elucidate the interpersonal aspects of internalizations. Also, these modes, derived from clinical observation, are now used to redesign Rorschach and TAT tests as diagnostic and predictive instruments. This part of the project, carried out in cooperation with Dr. Margaret Singer, is still in the pilot phase.

Further, the above conceptual framework allowed a comparison of group fantasies and family myths, opened up new perspectives on countertransference processes in the family therapy with adolescents, on psychoanalytic approaches to schizophrenia, and illuminated the phenomenology and dynamics of shame and guilt in the separation process of adolescence.

It appears now that at least one more year will be needed to make use of the rich data and insights which this project is yielding. While working on the above project, Dr. Stierlin has pursued various other lines of interest, more or less related to the above inquiry, of which some have been mentioned in previous reports. These include further work on a book on psychological exploitation and liberation with a major focus on how these phenomena affect, as well as reflect, concepts of human needs, power, and interpersonal justice. Dr. Stierlin has also taken up his interrupted work on Karl Jaspers and concluded it with a paper entitled "Karl Jaspers' Psychiatry in the Light of his Basic Philosophical Position." Related themes were covered by a chapter on self-actualization and philosophical awareness, and a paper on the German poet Hölderlin.

PSYCHIATRIC ASSESSMENT SECTION

William Carpenter, M.D.

The work of the Psychiatric Assessment Section has been carried out under difficult circumstances throughout the year. The failure to appoint a Chief for the Adult Psychiatry Branch, and the continuation of uncertainty about the Section's future support, necessitated considerable time and energy to administrate the Section, protect its resources, and support the morale of its staff and clinical research unit. The slot vacated by Dr. John Strauss in June 1972 could not be filled since authority to recruit a permanent senior staff research psychiatrist was withheld pending appointment of a Chief of the Adult Psychiatry Branch. Dr. Carpenter, therefore, served as both Acting Chief of the Section and Chief of the 4-East Clinical Research Unit. Because of the hiring freeze, we were without one of our two research assistants during the second half of the year.

Long-range planning for the Section's participation in collaborative work with the World Health Organization and within the context of the US-USSR Health Agreement became complicated and limited by the decision to assure the Section support only through June 1974.

The primary goals of the Psychiatric Assessment Section under Dr. William Carpenter, Acting Chief are: (1) to develop diagnostic concepts and categories that will have more meaningful relationships to etiology, course of illness, and response to treatment than diagnostic systems currently in use; (2) to search for objective validating criteria for diagnosis; and (3) to conduct psychobiological investigations in acute schizophrenic patients.

The need for improved diagnostic categories has been amply documented by the numerous research efforts in the epidemiology, treatment, psychophysiology and biochemistry of psychiatric disorder that have been hindered by the lack of reliability and validity of the currently used diagnostic categories. The staff of the Psychiatric Assessment Section employs standardized, detailed clinical assessment techniques, alternative diagnostic models, cross-cultural comparisons of psychiatric syndromes, and measures of course of illness, to develop more meaningful diagnostic categories.

At present psychiatric diagnostic categories are not validated by objective criteria. Course of illness has not proven as satisfactory as once hoped. The use of relative's psychiatric histories (genetic loading) and drug response as validating criteria are promising approaches, but still early in their development.

Psychobiological investigations of schizophrenia have rarely been accomplished in severely disturbed, early illness, drug-free patients who have been evaluated with sophisticated clinical research methodology. Such a clinical research unit has been established by the Section.

International Pilot Study of Schizophrenia: One major activity of the Section has been participation as the United States Field Center in the International Pilot Study of Schizophrenia (IPSS) sponsored by the World Health Organization. Other collaborating centers in this project are located in Colombia, Czechoslovakia, Denmark, India, Nigeria, Taiwan, the United Kingdom, and the USSR. The goal of this study is to develop and utilize cross-culturally applicable interview schedules for the evaluation of psychiatric patients in different countries. These schedules can then serve as a basis for future studies of comparative epidemiology and the cultural and biological factors in psychiatric disorders. Collaborating investigators from the centers have cooperated to develop the interview schedules for eliciting information on current psychiatric status, psychiatric history, social functioning, and demographic background and status, at time of follow-up examination. To accomplish this, schedules were written, pretested, revised and retested until they were suitable for use in all of the participating countries.

Data have been collected by interviewing 1,202 patients in the participating countries. Two-year follow-up interviews have been performed on these patients using forms developed in the study for evaluating course of illness and changes in social functioning. Information obtained from the follow-up investigation will provide a basis for comparing the course of illness of patients with different symptoms and different forms of treatment in culturally diverse countries.

In this study, standard psychiatric assessment techniques have been used for the first time in both initial evaluation and follow-up on a large scale by local investigators in several different parts of the world. Cross-cultural data on similarities and differences of patients from these countries have been obtained. The data analyses on the initial evaluations have been carried out and the Report of the IPSS, Volume I, was published in April 1973. Data

analyses of the follow-up interviews have been started and drafting of Volume II of the report has begun. The five-year follow-up evaluation is planned in eight countries for 1973-74, but participation by the United States is doubtful unless the necessary security and resources for the Section are provided.

Methodology for Analyzing Data for Psychiatric Diagnosis: The Psychiatric Assessment Section, together with Dr. John Bartko of the Theoretical Statistics and Mathematics Group, has evaluated adapted clustering techniques for defining types of psychiatric patients. Such clustering techniques are minimally influenced by theoretical bias, and let the data itself define the "natural groups" that constitute the patient population. The application of cluster techniques to psychiatric data poses many serious problems arising from both the mathematical properties of the techniques used, and the way in which clustering techniques reinterpret the usual clinical diagnostic modes. In the past year, the investigators have defined more clearly the nature of these problems, and explored modification that will provide more useful applications of cluster analysis to psychiatric diagnosis. Cluster analytic techniques applied to the IPSS patients have revealed interesting patient groupings. They suggest alternative subgroupings of schizophrenic patients. Affective psychoses are readily identified by cluster analysis and this approach also supports the diagnostic concept of a schizo-affective schizophrenia category.

Comparative Study of Diagnostic Systems: Different diagnostic systems are being evaluated using past psychiatric history and follow-up status as criteria for the validity of diagnostic types. At first, four diagnostic systems were investigated: (1) clinical diagnoses using the APA Diagnostic Manual; (2) computer-derived clinical diagnoses developed by J. K. Wing in London; (3) Lorr's Psychotic Types based on the In-patient Multidimensional Psychiatric Scale; and (4) clusters of psychiatric patients developed from the cluster techniques described in the preceding paragraph. Results indicated that none of the four diagnostic systems were able to predict significantly two-year follow-up status or to postdict earlier psychiatric history. On the other hand, use of multiple regression techniques demonstrates that prognostic items correlate highly with follow-up status. These results replicate results of other studies regarding the relationship of past history to future outcome, but also suggest the lack of utility of several diagnostic systems for the prediction of outcome. These findings suggest that dimensions of function are more important than diagnostic systems and symptomatology in determining outcome in schizophrenia.

To further evaluate other diagnostic systems, the criteria of schizophrenia by Kurt Schneider were used to classify American IPSS patients and NIMH manic-depressive patients. This first empirical test of Schneider's diagnostic system, which is accepted throughout most of the world, refuted his claim for pathognomonic symptoms in schizophrenia. This finding has now been replicated using data from each of the eight other countries participating in the IPSS.

Schneider's approach to the identification of schizophrenic patients has distinct advantages. Analysis of variance in the IPSS data has allowed a new group of highly discriminating signs and symptoms to be incorporated into a more flexible diagnostic system which will permit researchers to generate comparable groups for schizophrenia studies and clinicians to diagnose more reliably.

Another diagnostic concept of schizophrenia widely used, especially in Europe, was evaluated in terms of the IPSS data. Langfeldt's concept of schizophrenia has been extensively used, especially in the Scandinavian countries, and many studies have demonstrated its ability to select a poor outcome group of schizophrenics. In an attempt to replicate these findings, the Washington patients of the IPSS cohort were classified according to Langfeldt's criteria. The two-year outcome of the patients categorized as schizophrenic in this way was compared to the two-year outcome of the rest of the cohort. No significant difference was found in the outcome status of the two groups. This finding challenges the frequently accepted conclusion that the Langfeldt criteria of schizophrenia are adequate to define a disorder with poor outcome, and suggests that failure to control for such factors as duration of illness prior to initial evaluation has been a hidden determinant of outcome in these earlier studies.

Together, these findings regarding the validity of different diagnostic systems suggest that new concepts of schizophrenia must be considered. A dimensional concept of schizophrenia appears to be more valid than a typological concept.

In July 1971 the Psychiatric Assessment Section assumed administrative responsibility for a clinical research unit and established a research and treatment ward for acute psychotic patients. A clinical research methodology has been established to be conducted in acute schizophrenic patients during a severe psychosis, on recovery, and at one-year follow-up. This patient population is uniquely valuable for schizophrenic research because detailed and systematic clinical assessment is undertaken and the patients are studied during sustained drug-free periods. The treatment program is based on intensive psychological and psychosocial intervention, and has had notable success in treating and managing this difficult patient group.

Standardized clinical instruments have been developed to provide a coordinated system for evaluating patient symptomatology and behavior. A shortened form of the Present State Examination originally used for the IPSS, a daily nurses rating scale, a modification of the Katz Adjustment Scale and several special schedules are used to provide comparable data on patients from different sources of information. These scales collectively have provided a reliable and comprehensive source of information about clinical characteristics of patients. As part of these evaluations, Dr. Michael Sacks has compared the one-hour evaluation interviews with the entire data collection of the first three weeks of the admission period to determine the strength and weakness of the single research interview which is now being so widely used. Initial findings suggest that, while information from both the research interview

and the larger source of data often result in the same diagnosis being given to a patient, certain aspects of the evaluation interview appear to be inadequate for indepth clinical studies. Ratings of patient behavior from the one-hour interview consistently and significantly indicate less psychopathology than similar ratings made from all information available from the three-week evaluation period. This discrepancy is especially important in comparing simple schizophrenic and catatonic schizophrenic patients on the basis of a single research interview.

In a continuing attempt to validate different syndrome and diagnostic types, the clinical characteristics of the patients on the research ward are being compared to several biochemical, psychophysiological, and psychological variables. Leukocyte abnormalities, claimed to discriminate between normal, neurotic and psychotic patients by investigators from Prague, are being evaluated in an attempt to replicate this work, and to determine more precisely what symptom patterns relate to leukocyte abnormalities. Preliminary results fail to replicate the Prague findings. Steroid assays are being conducted by Dr. Edward Fink, to understand the relationship between patient symptomatology, classification, steroid changes, and patient outcome. Cortisol excretion is used as a biological indicator of stress and is being compared with clinical ratings as a variable, especially in psychophysiologic investigations.

Ms. Harriet Wadeson, an art therapist in the Section, is evaluating the relationship between art productions, symptom types and course of illness. Systematic collection of art data is proving valuable as a phenomenologic tool. Dr. Sacks has devised a method for evaluating a patient's course of illness in terms of his ability to participate in research. Dr. Sacks has defined three phases in the patient's view of a research task. We are determining the effect of each phase on testability and test results. There are important clinical and research implications to the three phases of delusional involvement in research procedures.

Collaborative studies of acute schizophrenia are being carried out with other investigators in the Intramural Program. Relationship between clinical characteristics and psychophysiological function is being studied in conjunction with Dr. Buchsbaum in the Perceptual and Cognitive Section (cortical evoked response and other tests) APB, Dr. Zahn in the Laboratory of Psychology (arousal), Dr. Williams, formerly of the Laboratory of Psychobiology (forearm blood flow), and Dr. Schooler in the Socio-environmental Laboratory (autonomic function). Studies of zinc metabolism have been carried out with Drs. Gillin and Henkin. Assessment of enzyme activity (transmethylase and platelet MAO) is being done with Drs. Wyatt and Murphy, Laboratories of Clinical Psychobiology and Clinical Science. Dopamine turnover is being determined with Drs. Goodwin and Post, Laboratory of Clinical Science. A system to discriminate between excited psychotic states is being developed with Drs. Ablon and Goodwin, Laboratory of Clinical Science. Comparisons of British and American diagnostic approaches are being conducted with Dr. Michael Schwartz, Laboratory of Clinical Psychobiology. Relationship between clinical characteristics, outcome, and psychological test data is being carried out in conjunction with Dr. Scott of the Section on Psychology, APB.

Collaboration outside the NIMH Intramural Research Program includes: (1) Dr. John Strauss, University of Rochester Medical School, on prediction of outcome in schizophrenia, evaluation of psychiatric history data, and other projects; (2) Dr. John Bartko of the Biometry Branch on profile analysis in clinical syndromes, on computerizing DSM II, and other projects; (3) Dr. Herbert Meltzer, Illinois State Psychiatric Institute, on the relationship between abnormal enzyme levels and clinical state; (4) Dr. Harold Himwich of the Galesburg State Research Hospital in investigating the transmethylation hypothesis; (5) Dr. John Gunderson of the Center for Schizophrenia Studies on the borderline syndrome; and (6) Dr. Fuller Torrey, Special Assistant to the Director, NIMH, and Drs. George Nemo, NINDS, and Lon White, NICHHD, on immunology and virology in schizophrenia.

SECTION ON PERSONALITY DEVELOPMENT

Roger Shapiro, M.D.

The overall objectives of Dr. Roger Shapiro and Dr. John Zinner in the Section on Personality Development continue to be investigation of individual adolescent personality development in the context of his family and of his social group. This investigation is done through study of a number of clinical situations in a residential treatment unit for adolescents where intensive work with families is also done. They are evolving a typology of families derived from observation of their interaction in conjoint family therapy. In particular, they are characterizing families of adolescents with borderline symptomatology, adolescents who do antisocial acting out and adolescents who are severely neurotic.

In addition, they are studying the group life of the residential treatment unit. Peer relations and authority relations in the inpatient group are studied in the weekly unit study group meeting; the relations of all the families to each other and to the staff are studied in the weekly multiple family meeting. These are situations in which observation is done of roles taken and given to individual adolescents as well as to families in a social context. These observations are central to the investigation of individual personality formation in the adolescent and its relatedness to group roles and family characteristics. They have concluded and are in the process of writing up the parallel investigations of normal adolescent group life in the school done at the Sidwell Friends School.

Dr. Zinner has interrupted studies of behavioral and physiological events investigated during conjoint family therapy sessions by the continuous monitoring of galvanic skin responses in family members and co-therapists. Mrs. Cabrera has continued the follow-up of patients' studies in the Section's research and treatment program, attending to both the condition of the index patient on follow-up and to the quality of the parents' marriage. Dr. Shapiro and Dr. Hauser are continuing the longitudinal assessment of cognition and identity formation in early and late adolescence, contrasting the performance of adolescents in the patient sample and non-patient adolescents at Sidwell Friends School.

All of these studies have suffered in significant ways during the past year because of uncertainties over future support for this program. It is an extensive program including work with disturbed as well as healthy adolescents, and including a variety of experimental procedures as well as clinical work. It has been impossible to continue work in all of these areas without some evidence that continued support for this work would be forthcoming. It was necessary to sharply and prematurely interrupt several research projects in order to maintain the program of family research and treatment on Unit 3-West. With Dr. Wynne's departure and Dr. Stierlin's withdrawal from participation on Unit 3-West, senior staff responsibility for the clinical program remained entirely with Dr. Shapiro and Dr. Zinner (in collaboration with Dr. Reiss). In consequence, during this year they have had to concentrate upon clinical research on Unit 3-West and have had to discontinue almost all of their work with healthy adolescents in the Sidwell School setting. Even on the psychiatric unit itself they have had to curtail important aspects of their research program. The study of psychogalvanic skin response in family therapy was interrupted. Research started by Dr. Reiss on the behavior of families in the multiple family meeting had to be curtailed. This has resulted in serious problems of morale in the research and clinical staff and strenuous efforts have had to be made to maintain a high standard of patient care on Unit 3-West. This has been done despite the difficulties being described.

In short, this has been a very difficult year with uncertainty about the program's future, attrition in the number of senior staff responsible for the clinical program, and premature termination of several promising research programs, all of which has resulted in serious morale problems and has greatly reduced the scope of the research program.

1. Treatment of Disturbed Adolescents and Their Families

Study of families of borderline adolescents, of antisocial acting-out adolescents, and of neurotic adolescents is done through observation of conjoint family therapy, of marital therapy of the parents, and of intensive individual therapy of the adolescent. Excerpts of family interaction containing defensive delineations of these adolescents by the parents provide evidence about the psychodynamic characteristics of the family and the unconscious assumptions of the family as a group. Data from the individual psychotherapy of the adolescent are the basis of formulations about the state of the ego in the adolescent, his capacity for object relations and level of defensive organization.

Comparison of families of borderline adolescents, antisocial acting-out adolescents, and neurotic adolescents reveals clear differences in the psychodynamic mechanisms determining defensive delineations of the adolescent by the parents. Parents of borderline adolescents manifest primitive splitting and projection of badness as the dominant mechanisms underlying defensive delineations of the index adolescent. In our series this is true for at least one of the parents, the parent most involved with the adolescent; the other parent may not manifest the same dynamic in delineation but is regularly

acquiescent to the splitting and projecting parent and does not provide a corrective experience for the index adolescent. Unconscious assumptions dominated by splitting and projection are inferred in these families.

Parents of antisocial, acting-out adolescents are more differentiated than the parents of borderline adolescents. Projective mechanisms are the basis of defensive delineations, but the projections are less massive and are likely to be differentiated aspects of impulse life like particular forms of sexual behavior (e.g., promiscuity, homosexuality) with more differentiated superego responses being retained within the parents. Unconscious assumptions are relatively differentiated unconscious fantasies which differ from family to family but contain in them fantasies originating in one or both parents (e.g., fantasies of promiscuity, homosexual fantasies, etc.) which are projected by the parents into the adolescent.

Parents of neurotic adolescents employ predominantly repressive defenses rather than projective defenses. In their defensive delineations of the adolescent they remain oblivious to major areas of behavior in the adolescent which would otherwise be conflictful for the parents. Their behavior toward the adolescent is frequently dominated by repression of conflict at the Oedipallevel in themselves, leading to repressive defenses in delineation of the adolescent in areas of sexuality, competition, and competence. Unconscious assumptions of the family as a group may be inferred which have differentiated and elaborated Oedipal themes.

As a typology of families of borderline, antisocial acting-out, and neurotic adolescents is articulated in this work, it supports a conceptualization of emotional disturbance arising from family and group dynamics rather than a conceptualization of disturbance arising in the separate sick individual. Understanding of disturbance in an individual as a manifestation of disturbance in a family counters the tendency in families and in the community to scapegoat individuals by isolating them as sick and attempting to locate all disturbance in them. This work constitutes evidence against the current unfortunate and reactionary tendency in psychiatry to isolate sickness in the individual and to conceptualize mental disturbance in a way which tends to exclude consideration of the families in which disturbance develops and the society in which it exists.

In the next year it is anticipated that current work with families of borderline, acting-out, and neurotic adolescents will be terminated because of changes in branch leadership. During the next year there will be a phasing out of the clinical program, and several new publications on the findings outlined above will be completed.

2. Longitudinal Assessment of Cognition and Identity Formation in Early and Late Adolescents

Dr. Stuart Hauser has continued as a consultant to Dr. Roger Shapiro to complete the investigation of cognition and identity formation in early and late adolescents of both sexes who are of patient and nonpatient status.

Several contrasts of interest are built into the design; patients-versus-non-patients; early-versus-late adolescents; male-versus-female adolescents; and each of the main groupings (patients and non-patients) can be subdivided in terms of sex and age for intra-group comparisons as well. All of these subjects have been studied over a two-year period.

The instruments for studying the subjects include a self-image interview, a Q-sort, and a battery of cognitive tests. The Q-sort is a major technique of the study as it focuses on self-images. Modifications of the Q-sort Technique developed for this project make it possible to focus more intensively on dimensions of each self-image as well as overall integration and changes in self-images are being analyzed at single points in time, and over spans of time.

The cognitive tests focus on processes of categorization, differentiation, conceptualization, and problem solving. The cognitive data are being analyzed in terms of sub-sample differences at single points in time and change over time. In addition, correlations, and parallels, between self-image results and cognitive results are being done.

3. The Family Psychophysiology Project

Clinical studies of family interaction carried out by Dr. Zinner have revealed the important role of anxiety as a subjective experience which mobilizes and determines behavior within the family group. Customarily, behavioral observations are of the moment-to-moment verbal and non-verbal transactions within the family. On this time scale, anxiety is an elusive variable. This area of private subjective experience on a time dimension which would match that of our behavioral observations has been monitored by Dr. John Zinner, with the assistance of Mrs. Deborah Runkle, using the galvanic skin responses (GSR) of family members during family therapy sessions. This year a quantitative analysis has been completed of verbal and physiological events in a study of a group of families monitored at different times during their treatment, and the project has been interrupted.

4. Follow-up Study of Families Treated in the Study of Adolescent Identity

More than half of the families treated in the study of adolescent identity have been re-interviewed after varying periods of time following termination, and this follow-up is continuing. Special attention has been directed to evaluating and interpreting the long-term meaning of the program for the parents who were in couples' treatment as well as the adolescent. In reports prepared on this study, Mrs. Carmen Cabrera has described the course of couples' therapy and its impact over time. She has found a correlation between improvement in the emotional life of the adolescent and in the marriage relationship of the parents. Mrs. Cabrera is interviewing the remainder of the sample to continue and expand upon earlier findings.

SECTION ON TWIN AND SIBLING STUDIES

Richard Wyatt, M.D.

The last year has been a productive one for the Section on Twin and Sibling Studies. Dr. William Pollin who had been Chief of the Section since its inception was asked to take on three roles in the Extramural Program of the NIMH. These roles included coordination of Area B the NIMH Research Task Force, studying the research engaged in by the NIMH, a member of the United States Committee on Schizophrenia involved in interchanges with a similar committee of the Soviet Union, as well as an administrative position in the Division of Narcotics Addiction and Drug Abuse. Because Dr. Pollin's new administrative roles required a large proportion of his time, he proposed that Dr. Richard Wyatt act in the unofficial capacity as coordinator of the Section's work during the last year. This was accepted at both the Branch and Division level and Dr. Wyatt has acted in that capacity during 1972-1973. The year has thus been one in which the Section moved in two directions; that previously envisaged by Dr. Pollin, as well as a new one begun by Dr. Wyatt.

Despite what would appear to be an ambiguous administrative arrangement, the staff of the Section has worked extremely hard, creatively, and productively. The major project undertaken by the Section during the last year was based on tools developed by this Section in the past. Identical twins discordant for schizophrenia had previously been used in attempts to parcel out the effects of heredity from environment. In 1972, two enzyme abnormalities were described in the platelets of schizophrenic individuals. One of these was a deficiency in platelet monoamine oxidase, an extremely important enzyme in the metabolism of biogenic monoamines. Researchers in the Section, along with Dr. Murphy in the Laboratory of Clinical Science, found that both schizophrenic and non-schizophrenic co-twins had the platelet abnormality. This indicated that the abnormality is genetically determined rather than being secondary to environmental factors which might accompany the schizophrenic process, such as the exposure to drugs, chronic hospitalization, and unusual diet. In addition, there was a high correlation between schizophrenic and non-schizophrenic twins which also indicated that the enzyme abnormality was genetically controlled. The Section believes that this is the first demonstration of an enzyme abnormality in schizophrenia which is genetic in origin and represents an enzymatic marker for the vulnerability to schizophrenia.

The second enzyme abnormality that was studied was in an enzyme capable of forming the hallucinogen, dimethyltryptomine (DMT). This enzyme had previously been found to be elevated in schizophrenic and other psychotic individuals. Again the twin model was used for studying this enzyme abnormality. The DMT forming enzyme activity was found to be elevated in the schizophrenic and not in the non-schizophrenic twin. Because of this, it is thought that the enzyme abnormality was environmentally rather than genetically controlled.

In addition to the biochemical studies, the twins were extensively interviewed at the time bloods were drawn. This follow-up study, some eight years

after the subjects had initially been contacted by this Section, indicated that there was a minimal concordance rate within the group of 6.3% while there was a possible maximum concordance rate of 25%. This indicates that the monozygotic twins discordant for schizophrenia are a relatively stable group with regard to their concordance.

An important study into the psychological precursor of cardiovascular disease was begun in collaboration with the National Heart and Lung Institute. It is hoped that we will be able to predict, using criteria developed by Dr. Ray Rosenman at the Harold Brunn Institute for Cardiovascular Research in San Francisco, which persons having Type II hypercholesterolemia are coronary prone and which are not. Subjects are being interviewed by Dr. Robert Belmaker with a standard technique and are rated into those with a high drive (Type A) and those with an easier manner (Type B). This will be correlated with independent studies of coronary heart disease.

A longitudinal study of ten sets of twins followed since birth by this Section is being carried out by Drs. Martin Allen and Stanley Greenspan. They are administering psychological tests in order to provide information regarding hypothesis about genetic and non-genetic antecedents of personality. In a related project, Mrs. Eleanor Dibble of this Section and Dr. Donald Cohen, now at Yale Child Study Center, are carrying out the Childhood Personality Development Study in a group of over 300 pairs of twins. The vast amount of data generated in this study are currently being compiled and analyzed. It is hoped that the present arrangement which has been so productive during the last year will be able to be continued for one more year. The major thrust of the next year will be to finish the coronary predictive project and the personality project of twins. The longitudinal follow-up of the ten sets of identical twins is scheduled to go on for many years. The major thrust, however, of the Section during the next year, if present administrative arrangement can be continued, will be to inquire into the nature of the genetic abnormality of platelet monoamine oxidase in schizophrenic patients. Such things as the structure of the protein, how the enzyme abnormality is transmitted from one generation to another, and whether the abnormality is causative of the illness are underway.

SECTION ON EXPERIMENTAL GROUP AND FAMILY STUDIES

David Reiss, M.D.

The scientific work of this Section was sharply curtailed during the past year by a number of factors. First, its Chief, Dr. David Reiss, assumed a significant increase in administrative responsibilities by taking the positions of Acting Branch Chief and member of the NIMH Research Task Force. Secondly, Nursing Unit 3-West, a major source of subjects, was forced to stop admitting new patients owing to uncertainty about its future. Third, the Section required, but did not obtain, an additional research assistant (it had only one for many years); indeed a research assistant was hired, trained at considerable cost of time and energy to other Section staff members, but could not be retained because of inattentive personnel practices and the hiring freeze. Fourth, the major and continuing uncertainties about the future of the Branch made it impossible to work out a reasonably long-term and stable cooperative arrangement with our important research collaborator, the Psychiatric Institute of Washington. Thus, systematic data collection from that Institute, as of the time this report is submitted, has not even begun. It is indeed regrettable that these factors have combined to seriously damage the progress and development of the Section's work at a time when its methodologic and theoretic advances of the previous four years made major and significant progress extremely likely. The irony is compounded by the fact that this past year was the first full year that the Section's new laboratory was fully-equipped and ready for extensive use. Despite these obstacles and frustrations significant work continues along two converging lines of investigation.

Both lines of investigation are attempts to study the subtle and manifold relationships between the family and its social environment. The model system for this study was the psychiatric ward and families of its in-patients. Indeed, many of the Section's studies have been attempts to demonstrate the effectiveness and precision of the research ward as an instrument for psychosocial studies. In the first line of investigation, the Section has sought to characterize those aspects of the ward social community that are most likely to influence process and structure in families admitted to them. For these studies, the Section has relied mostly on paper and pencil tests of personality atmosphere and value orientation of the psychiatric staff. The second line of investigation has sought methods for studying the family's integration into the ward community. The overall progress of the work, method and specific hypothesis has been guided by a theory of consensual experience in families, developed in the Section's previous work, and by a theory of social values of Kluckhohn, Strodtbeck and Almond.

The Study of Social Values on a Psychiatric Ward. Evidence collected by this Section and by a wide variety of other investigators indicates that complex organizations and social systems have a profound impact on the interaction of small groups (including families) of which they are composed. A major mechanism for this influence involves the social values of the larger social unit. Evidence collected in the Section's laboratory suggested that values

of social community usually are transformed into clear-cut and controlling norms for social interaction in small groups. Interaction patterns are shaped by these norms in a variety of ways and can have long-lasting impact on the structure and process of the small groups (including families). This year the Section has sought to investigate the character of these values by the use of a variety of paper and pencil tests. Specific questions have concerned their stability over time, their uniformity within an institution and across various role segments (psychiatrists, nurses and patients) within a given ward community. We have also investigated the relationship of ward values to the personality structure of ward staff and the contribution of these ward values to the perceived or experienced ward atmosphere (as it may be sensed by a stranger or newcomer to the ward scene). Had more stable support for our investigations been forthcoming, the Section would have investigated the precise role of social values in mediating the influence of the social community on family structure and process. Our first phase of data collection is completed and data analysis is in progress.

Family Interaction with the Social Community. Previous investigation in the Section's laboratory suggests that a family's adaptation to a new social community is a two stage process. First, the family's collective response is determined by a stable, collective disposition we have called typical consensual experience; this determines whether the family will actively explore its new surroundings or retreat from it and, also, if it explores its new surroundings how it will interpret the data. Second, as a result of explorations, c o nditioned by its basic collective disposition, the family forms a shared construct of its immediate social environment. This shared construct determines its collective interaction with other families and staff. The Section's investigators suspect that ward values may alter this construct in some families indirectly by determining the form of its preliminary investigations but this aspect was not directly studied in the present investigation. If the theory is correct one should be able to predict specific family constructs from knowledge of its basic, collective dispositions. The latter can be measured by the oft-used laboratory procedures, particularly the family pattern recognition task. For the former, the investigators developed two new procedures: the family perception test (which tests a family's construct of other families on the ward) and a ward perception Q sort which tests the family's construct of the ward as a unitary social community. A second test of the theory is to use the family construct data to predict the pattern of interaction between the family and ward. The latter is measured by objective verbal and non-verbal indices also developed specifically for this study. During the year all the procedures were developed into their final form and data collection began only to be aborted by the many obstacles already described. The future of this most promising project is in grave doubt.

SECTION ON CLINICAL PSYCHOLOGY

Winfield Scott, Ph.D.

Since the beginning of its work, the Section on Clinical Psychology has had two main emphases in research activities. The first has been on the study of the family as a small group; the second has been on individual psychodiagnosis. All research activities have been rooted in clinical involvements with individual patients and families. There has been such an intimate relationship between clinical and research activities that the same contacts with patients and families have often served as a source of both clinical and research data. In collaboration with investigators from other units, data have been derived from various sources including laboratory measures of perceptual and cognitive functions, and standard and experimental psychological tests. Subjects have ranged from individual patients with psychotic, neurotic and characterological impairments, to patients with diagnosed or suspected neurological impairments, to patients being treated with a variety of experimental drugs, to non-psychiatric volunteers.

On January 1, 1973, Dr. Winfield H. Scott, the Chief of the Section, began work on a part-time basis at the George Washington University Medical Center, with a joint appointment in the Department of Medicine and Psychiatry. On July 1, he will begin to work there full time resigning from his role as Chief of the Section on Clinical Psychology. With his departure, and with the shifts which are likely to occur in the nature of the 3-West program, one of the two main lines of research which have been carried out--research on the psychological study of the family as a small group--will end. The fate of the other line of research, on individual psychodiagnosis, will depend upon decisions to be made by the remaining members of the Section, and will be affected by reorganization of resources, reallocation of personnel and revision of goals in the Adult Psychiatry Branch, with the imminent shift in command.

In the study of the family as a small group, the major research activity during the past two years has involved administration of the Consensus Rorschach to families of psychiatrically impaired adolescents, followed by playback of video and audio recordings of the sessions to the families, and subsequently by retesting to assess the effects of the procedure on task performance and on self-image. Applications of the approach for clinical assessment of families have been explored. At the same time, systematic research has been underway on the differentiating features of families of psychiatric patients, and on the effects of a variety of "feedback" conditions on both task performance and self-image. Four members of the family, including the parents, index patient and a sibling, have been met in a series of three sessions. During the first session, the Consensus Rorschach has been administered. In this procedure, families are asked to see how many agreements they can reach about what an inkblot looks like. During the second session, depending upon the assignment of the family to one of several different experimental conditions, family members view a videotape or listen to an audiotape made during the first session, studying the relationship between interactional process and test product. During the final session, families

have been retested with both the Consensus Rorschach and paper and pencil psychological tests and questionnaires. Because the experimental aspects of the research are dependent upon 3-West as a source of subject families, and no new families are currently being admitted to that program, that aspect of the research--comparison of various aspects of contrasting feedback conditions--will not be completed. Writing based on clinical observations of the families is now in progress. It appears that families of psychiatric patients are regularly unproductive in the first Consensus Rorschach procedure, but that reasons for low productivity vary from one family to another and relate to salient features of the family as a small group, features which are likely to have effects on the functioning of its individual members.

In the area of individual diagnosis, research activities have included projects to study the relationship between performances on laboratory measures of perceptual and cognitive variables, and styles of responding to the Rorschach; studies of patients who are acutely psychotic, including not only schizophrenics but patients with affective disturbances and borderline schizophrenics but patients with affective disturbances and borderline schizophrenic conditions; and studies comparing patterns of deficit in intellectual functioning among patients with a variety of psychiatric and neurological impairments. Work has been completed on studies of the relationships between contrasting approaches to Rorschach responding and performances on laboratory measures of perceptual and cognitive variables.

For the time being, research will continue on studies of deficits in intellectual, personality and central nervous system functioning in contrasting groups of patients, including some with established central nervous system pathology, patients with acute affective disturbances and schizophrenics.

SECTION ON PERCEPTUAL AND COGNITIVE STUDIES

Monte Buchsbaum, M.D.

Under the direction of Dr. Monte Buchsbaum, the Section has deepened its studies of the neurophysiological basis of individual differences in the related areas of attention, habituation and stimulus intensity control and the relation of these variables to genetic and biochemical mechanisms. Working closely with members of the Laboratory of Psychology (Drs. T. Zahn and P. Wender), and in collaboration with the Section on Psychiatry, Laboratory of Clinical Science (Drs. F. Goodwin and D. Murphy), and the Section on Psychiatric Assessment (Drs. J. Strauss and W. Carpenter), clinical average evoked response (AER) studies of normal twins, patients with affective disorders and schizophrenia, and hyperactive and normal children have been carried out to complement basic investigations.

Based on genetic studies of normal MZ and DZ twins and clinical studies of medication-free patients with bipolar and unipolar affective disorders and schizophrenia, it appears that relatively enduring, genetic mechanisms are important in determining functional stimulus-intensity relationships of secondary (100-150 msec post stimulus) AER components. These components have high heritability and appear to distinguish patient groups such as bipolar/

unipolar or bipolar/schizophrenic even when levels of depression are matched. High platelet MAO was found with low AER amplitude-intensity slopes. Differences between men, women and 45XO patients are also found. Correlations with clinical behavioral ratings are relatively low. Changes with L-DOPA or AMPT administration, whether in man or monkey experiments (done at Illinois State Psychiatric Institute with George Borge, Eugene Redmond and James Maas) also seem relatively small.

In contrast, later AER components (150-250 msec post-stimulus) while also showing significant heritability, are less useful in distinguishing clinical groups of patients, but more highly related to clinical rating scales. Differences based on sex chromosomes were not found. Changes with alpha-methyl-paratyrosine (AMPT) and dopa were stirking in monkeys and in somewhat comparable human studies. Effects of amphetamine in hyperactive children also appeared in this time band. Detailed psychophysical experiments suggest that the earlier AER components related to expected properties of stimuli and general arousal; later components related to novelty, "meaning," "attention" and other complex psychological constructs. These are undergoing intense experimentation currently, and are discussed elsewhere. (See Laboratory of Psychology).

In several studies, AER measures proved to be associated with individual differences in drug response or clinical course; hyperactive children who had a positive response to amphetamine showed different AER patterns than children who did not improve; schizophrenic patients who showed "reducing" patterns tended to improve without phenothiazine therapy.

Unipolar patients who might be identified as bipolar on the basis of platelet MAO were also identified as bipolar on the basis of the AER. Intriguing individual differences seen in the monkey studies suggest that L-DOPA response variability might also be predicted. Taken together with the genetic studies, these findings suggest that the AER may have utility as a genotypic marker of pharmacologic response.

UNIT ON ART THERAPY

Mrs. Hanna Kwiatkowska

The systematic analysis of Family Art Evaluations conducted by Dr. James Dent and Mrs. Hanna Kwiatkowska was continued within the limitations of the time of the principal investigators, neither of whom are now formally associated with the Intramural Research Program.

Work on the cross-cultural comparisons with the Brazilian families was also continued and in particular with the assistance of Mrs. Junia Novaes a guest worker, graduate student from Brazil. It was possible to fill in missing data and clear up certain discrepancies in the data which have been delaying the study for some time because of communication and translation problems. The project "Sources of Variance in Cross-cultural Application of the Techniques of Analysis" also progressed, thanks to her help. It is now reasonably clear that what problems of cross-cultural comparison there are, they are not

due to inaccuracy of translation into Portuguese. However there probably are some particular frames of reference which are not commonly shared by the two research groups.

Findings from the study of material from Family Art Evaluations with adolescents and their families on the 3-West Unit are being written up as a chapter in the book "Family Art Therapy" authored by Mrs. Hanna Kwiatkowska, and commissioned by Charles C. Thomas, Publishers, Springfield, Illinois. The study of this group of patients with nonpsychotic problems, such as delinquency, drug abuse and truancy, focuses on the ambivalence over separation of adolescents and their parents which is clearly revealed in their individual and joint art productions. It is also found that the hypotheses of other researchers on family dynamics of this group of patients are vividly represented and illustrated in the family art evaluation sessions.

The work of the Unit on Art Therapy continues to arouse interest in the United States and abroad. The graduate course in Family Art Techniques, taught by Mrs. Kwiatkowska, at the Graduate School of Arts and Sciences of the George Washington University in conjunction with the Washington School of Psychiatry attracts an impressively increasing number of students, including foreign students (from Japan and Israel). Numerous workshops and seminars based on the Family Art Techniques, as developed by this unit were conducted by invitation in the United States and abroad (Yugoslavia).

1973

Annual Report of the Child Research Branch

Division of Clinical and Behavioral Research

National Institute of Mental Health

Richard Q. Bell, Ph.D., Chief

This project, to which the entire Child Research Branch is committed, was launched in order to understand how preparental characteristics interact with congenital characteristics of children in producing social, emotional, and cognitive development during the early years of life. Since 1966 a large cohort of newlywed couples has been studied by separate teams of investigators that specialized in research on early marriage, pregnancy, early infancy, and the preschool period. Each team studied the cases without prior knowledge of the assessments carried out by the others. The study is now in the seventh and final year of data collection and all teams will shift in this coming year to analysis and reporting of the results. Though the initial sample of early marriages was much larger, samples for the phases after early marriage range from 100 to 130.

Most of the findings reported in each section's summary to follow are from preparatory studies carried out to test procedures and refine concepts relevant to the project involving the main cohort. The fact that findings from these preparatory studies alone have already had considerable impact on the field of family and child development is some indication of the rich reward we may expect from the main longitudinal study.

Some clarification of terminology will be of assistance to the reader before we proceed further. The term "within-stage" refers to data gathering or analysis within a period for which a given section is responsible. For example, the Section on Child Behavior carries out within-stage studies of the children during the month that they attend our research nursery school. Within-stage analyses for the Section on Infant Development concern only the first few days of life. Cross-stage analyses refer to longitudinal relations between the periods of early marriage, pregnancy, the newborn period, the third month postpartum, eleventh month postpartum, and the early preschool period. The terms "main cohort" or "main longitudinal sample" are used interchangeably to refer to the sample for which data collection was initiated in 1966 and is being completed this year. In contrast, shorter-term longitudinal or cross-sectional studies are collectively referred to as preparatory studies.

In the reports following that of the Office of the Chief, the reader will detect a great deal of concern with the process of primary data reduction, consisting of checking for coding errors, testing for observer agreement, and assessing short-term stability. There is also considerable

study of the interrelations of measures at a single phase of development, and an effort to locate factors. For those not familiar with the special problems of longitudinal research, it should be pointed out that these activities have common bases. First of all, the measures used to characterize our sample in each period must be quite powerful and precise, in order to overcome the substantial variable error due to uncontrolled events that occur between stages in the life histories of the cases. Efforts to test for internal consistency or short-term stability are vital to a longitudinal study because it is unlikely that long-term relations can be obtained from behaviors that are ephemeral in a single stage of development. By way of contrast, it should be noted that it is possible in an experimental study to demonstrate significant differences between two groups on a single measure, even though the cases within each group show no stable standings on the measure from day to day. In a longitudinal study, such a measure would have very little chance of showing relations beyond the period in which it was obtained.

One other method of checking data before carrying out cross-stage analyses is to relate measures to phenomena known to be operative or important in a certain period. For example, the section on infant development checks its measures of newborn behavior and physiology to see whether known characteristics of habituation can be found. They also study the relationship of these measures to drugs given the mother, in order to see whether factors specific to the newborn period are unduly affecting a measure. In other sections, checks on sex and social class differences within a stage offer a way of finding out whether the measures show the relationships that might be expected.

Organizing measures at each stage into sets contributes to the power of the longitudinal measures, since a composite score representing several measures is usually much more reliable than the single components. Furthermore, the number of cases available for cross-stage comparisons is seldom sufficient to allow cases to be dropped from an analysis because of occasional missing bits of information. A composite score representing a factor can be computed for each case, even though some of the elements of the composite are missing for some subjects.

In short, each research team at this point in data analysis has had to give much more attention to the psychometric qualities of their data than would be the case in most non-longitudinal research being carried out in the field of child development.

Office of the Chief

The second biennial report on the status of the longitudinal study has been prepared and will be distributed to major investigators in the field of psychology, psychiatry, sociology, social work, marriage and family life, and pediatrics. The report briefly describes current research, and lists reports from previous years, organized so that the reader knows whom to contact within the branch to receive a copy of the complete article.

Personnel in the Office of the Chief are well into the second step of organizing our data bank for the main cohort. Having completed the first step of indexing test procedures and interviews that have been obtained for all subjects in all phases of the study, it has been possible this year to place most of the data from the marriage study in a central branch data bank, with copies in federal storage, or in computer-tape form in different computer facilities, so that fire or accidents cannot cause loss of the material. The data from each other section will be similarly treated.

Scientific activities of the Office of the Chief were as follows: During the summer I attended the 20th International Congress of Psychology in Japan, contributing to a symposium on the topic of continuities and discontinuities in personality development. At this conference I made contact with a team of Japanese investigators carrying out a longitudinal study in Hokkaido. They are covering part of the age range of our own study, and are also concentrating on the early mother-infant relationships. After returning from Japan, I presented at various university colloquia a paper that sets forth some preliminary guidelines toward a theory of how infants and young children affect parents. This latter paper was developed sufficiently by October that I used it as the keynote address to a conference held at Princeton on the topic of the effects of human and animal young on caregivers. In January, at the Winter Conference on Brain Research, I presented a paper describing the varieties of metamorphic and isomorphic relationships that have been reported in longitudinal studies of early infancy at our own and other centers. In April I was elected to the governing council of the Society for Research in Child Development.

Throughout the year I have met with various committees of the federal inter-agency panel on early childhood research and development. One result stemming from these meetings is that other agencies have reported an interest in applying some of the findings from our longitudinal study to their intervention programs. One other result of the meetings is that an inter-agency panel is acting on a recommendation I made that there be an effort to develop marker variables to be used in future research for various areas and age ranges in early development. With such variables, findings from federally supported research could be aligned and interpreted more readily, and progress toward establishing stable, consistent and well agreed upon findings may be accelerated. I found considerable support amongst members of the panel with a concern I expressed that changes in society, in child rearing, and in family life, may be occurring more rapidly than social science is able to develop solid findings that can guide national policy.

Section on Family Development

This research team continues in a phase of data analysis and reporting. New computational methods developed this fiscal year include specialized item analysis procedures, and specialized procedures for rotating and comparing factor analyses. Analysis of interaction data from the Color Matching Test has been completed this fiscal year, and has led to the development of four conceptual dimensions for describing interaction in young couples.

Several lines of work started last year were completed and published this year, including a paper by Kafka and Ryder on marriages in the "counter culture" and a paper by Ryder describing changes in reported marriage satisfaction as a function of having a child. Olson has ventured some predictions concerning the future of marriage, and these are also presently in press.

The work of creating manageable and accurate files from the massive sets of data collected by this team has been essentially completed this year, so that efforts can now be devoted to substantive analyses.

Section on Parent-Infant Behavior

Except for factual material derived from pregnancy and postpartum interviews (that has been coded but not yet processed further) the data on the main longitudinal sample collected by this section have been placed in form for computer processing. Much time has been devoted to revising codes, inspecting print-outs for errors, and in correcting computer programs. It was necessary to use three observers because the sample was large and the time spent in home observation was so extensive. Thus, it has been necessary to determine if there were true recording differences between observers, or simply inadvertent sample differences. This evaluation has been carried out in the case of each variable, in order to determine whether standardized or raw measures should be used for home observation data.

With the foregoing tasks essentially complete, it has been possible to turn to within-stage relations. We have gleaned the following findings from pregnancy interviews and home observations. Mothers from homes of upper socioeconomic status (SES) were rated from the pregnancy interviews as significantly higher on variables having to do with intimacy and affectionate contact, social interaction with the infant, general stimulation of the infant, and identification with the maternal grandfather. The lower SES women, on the other hand, were rated higher on variables measuring depression during pregnancy, apprehension over health and well-being of the infant, and degree of generalized apprehension. Furthermore, correlations between the pregnancy ratings and later maternal behavior recorded in home observations tended to be significantly related only for the upper SES mothers. These are tentative findings but they at least suggest caution for those who may have hoped that a general theory of socialization can be developed. There is also some implication that economic pressures work to attenuate in lower SES mothers the patterns of mother-infant relations that would otherwise develop over time.

Also, we now have available from our first sifting of the data a comparison of second-born infants and their first-born siblings, using three month home observation variables. Apparently, mothers spend more time caretaking and engaging in social-affectionate interactions with their first-born than with their second-born offspring. On the other hand, the second-borns received more physical stimulation.

Section on Infant Development

In the past year the Section has completed its task of data reduction and transformation. The within-stage stabilities of a large portion of the measures have been established. Three issues are currently under investigation, one of which is a continuation of analyses begun in 1972. That issue involves behavioral and heart rate responses to repetitive threshold presentations of a tactile stimulus. Results not only indicate that response decrement occurs rapidly at threshold levels, but also suggest that cardiac-somatic coupling is present in the newborn. The second issue involves the relationship between drugs given a mother during labor and the behavior of her infant immediately after birth. Preliminary analyses have failed to confirm the frequently reported finding that increasing dosages of drugs given the mother are associated with increasing degrees of depression in the newborn. The third issue concerns Waldrop and Halverson's report of an association between minor physical anomalies and hyperactive behavior in preschool age children. Currently under investigation is the possibility that these anomalies, stable from the newborn to preschool period, are related to various facets of newborn behavior. Our initial analyses suggest that if newborn characteristics are related to the anomalies, it will be in the form of combinations of measures, rather than single measures.

The upcoming year should see completion of the transformational computations, and reliability assessments of the data, as well as an assessment of the relationships between newborn characteristics. We will also have begun the task of relating newborn characteristics to earlier data on pregnancy and later data on infancy.

Section on Child Behavior

This Section has devoted the past year to finishing the study of the remaining cases from the main longitudinal sample. By July 1973 approximately 160 children will have participated in a series of studies at the early preschool period. The task remaining is to analyze the large amount of material collected on each case into a manageable corpus of concise measures. Within-stage analyses will focus on measures that are stable over various play settings as well as over time. Sex and social class differences will also be analyzed at the preschool period and related to the data collected earlier on the parents and children.

In this year's work on data from studies carried out previously (in preparation for the main cohort) Halverson has shown that our mechanical recorders yield stable individual differences in activity, that there is generality across settings for males, and that the measures are not only valid but also index behavior that has substantial unrecognized impact on judgments made by observers of children. The activity recorders have come into increasing use in the field of child development, and the findings published this year will be very helpful to many investigators.

In a study of peer relations over a five-year span, Waldrop has shown that the assertive, peer-oriented preschooler tends to be dominant and develop extensive peer contacts in the early school-age period, if a male, but shows intensive peer relations if a female. This is a fascinating and novel longitudinal finding in its own right, but also serves the useful purpose (as did the results from activity recorders) of sharpening our knowledge of how to treat the new set of data from the main longitudinal study.

Annual Report of the Laboratory of Clinical Science
National Institute of Mental Health
Irwin J. Kopin, M.D.,Chief
July 1, 1972 through June 30, 1973

Introduction

The Laboratory of Clinical Science consists of four sections (Pharmacology, Medicine, Psychiatry, and Experimental Therapeutics) and the Office of the Chief (which includes Units on Clinical Biochemistry, Clinical Pharmacology, Analytical Biochemistry, and Histopharmacology).

The programs of research conducted in the various sections and units of the Laboratory of Clinical Science are directed toward understanding the biological basis of a variety of psychiatric and neurologic disorders and how alterations in the fundamental processes of neuronal function which attend such disorders may be corrected by pharmacological or other interventions. The research efforts are, therefore, aimed toward elucidating the fundamental biochemical, neurophysiologic, and hormonal processes which control neuronal function and determining how drugs, humoral agents, genetic factors, and environment influence the development and function of the nervous system. Clinical investigations, directed toward describing pertinent biological abnormalities and providing new information about the effects of various therapeutics approaches on the course of psychiatric or neurologic disorders, are designed to take advantage of the newest discoveries in the laboratory and often stimulate new lines of fundamental investigation. The diversity of talent and individual approaches to research represented in the sections of the Laboratory provide an unique opportunity for productive interaction of clinical and more fundamental investigations.

Section on Pharmacology
Julius Axelrod, Ph.D.,Chief

The Section on Pharmacology has continued investigations on catecholamines, minor biogenic amines, the control of metabolism of amines in the pineal gland and the metabolism and disposition of psychoactive drugs.

Using a very sensitive isotopic assay for catecholamines which had been developed by Dr. David Henry, he and Dr. Joseph Coyle showed that norepinephrine and dopamine appear in the rat brain 15 days after gestation and rapidly increase 15-fold during the week before birth. The levels of these amines appear to be subject to the same control mechanisms in the fetus as in the adult. Explants of substantia nigra and corpus striatum from brains of newborn rats have been maintained in vitro and Drs. Coyle and Jacobowitz (Unit on Histopharmacology) have found that axonal

outgrowths from dopaminergic neurones maintained in cultures have properties similar to axones in the intact brain.

Enzymes for synthesizing and metabolizing the catecholamines are formed in the cell body and transported down the axon to the nerve ending. Drs. Wooten and Coyle have measured the rates of enzyme transport and found that dopamine-β-hydroxylase and tyrosine hydroxylase are rapidly transported, while catechol-O-methyltransferase and monoamine oxidase travel at a slow rate and dopa decarboxylase is transported at an intermediate rate.

Studies on dopamine-β-hydroxylase in human plasma have continued and Dr. Fred Wooten has found a marked increase in the level of this enzyme in patients with hereditary torsion dystonia of the dominant type, while those with the recessive form of the disease have low or normal levels of the enzyme. In mice, Dr. Roland Ciarnello has examined the genetic control of phenylethanolamine N-methyltransferase, (PNMT), the enzyme which forms epinephrine. He has found that the levels of this enzyme in the adrenal gland are controlled genetically by the rate of its degradation.

Drs. Saavedra and Axelrod have developed a sensitive enzyme assay for phenylethanolamine and phenylethylamine. The formation, metabolism and effect of drugs on these brain amines, as well as on tryptamine were examined. Tryptamine methylating enzyme was found in blood platelets. Studies in collaboration with Wyatt showed that this enzyme was elevated in blood platelets of schizophrenic subjects. Drs. Saavedra, Brownstein and Axelrod developed an extremely sensitive enzyme assay for serotonin, which makes possible examination of this biogenic amine in individual nuclei in brain.

Studies on the pineal with Drs. Deguchi, Brownstein and Holtz showed that N-acetyltransferase is rapidly degradated if the beta-receptor of the pineal is not occupied by a catecholamine. The beta-adrenergic receptor controls the circadian alteration in pineal serotonin synthesis as well as synthesis of N-acetyltransferase. The pineal beta-adrenergic receptor becomes more sensitive in the absence of noradrenaline and less sensitive in the presence of an excess of noradrenaline. The supersensitivity and tolerance appears to be due to changes in conformation of receptor rather than the formation of new receptor sites.

Drs. Kreuz and Axelrod have found that tetrahydrocannabinol, (THC), and some of its metabolites are highly localized in body fat and that, after repeated administration, THC and its metabolites accumulate in fat. A sensitive enzyme assay for measurement of amphetamine in human plasma has been developed and will be applied to study of the kinetics of metabolism of this drug in patients.

Section on Medicine
Irwin J. Kopin, M.D., Chief

Studies in the Section on Medicine continue to examine the mechanisms for control of catecholamine synthesis and their biosynthetic enzymes in the adrenal glands, sympathetic nerves, and adrenergic neurones in brain and to relate these to drug effects, environmental and genetic factors, and functional abnormalities as well as control of various autonomic functions (gastrointestinal motility, blood pressure) and neuroendocrine regulation.

The effect of adrenalmedullectomy on the response to cold stress of the enzyme content of the sympathetic ganglia has been shown by Dr. Ingeborg Hanbauer to be influenced by adrenal cortical hormones. In mice, the response of the adrenal medullary catecholamine-synthesizing enzymes to stress of fighting has been found by Dr. Maengwyn-Davies and her collaborators to vary with genetic factors and to be responsive to phenobarbitol and other psychoactive drugs. In rats, Dr. Friedhelm Lamprecht, et al showed that Δ^9 tetrahydrocannabinol, (Δ^9THC), the active constituent of marijuana, enhances the adrenal medullary response to immobilization stress. With Drs. Williams and Ng he has found that Δ^9THC reduces blood pressure in unstressed rats and prevents the elevation of blood pressure seen in immobilized rats. The intracerebral administration of 6-hydroxydopamine (6OHDA) prevents the elevation in blood pressure produced by administration of desoxycorticosterone acetate (DOCA) and salt diet. In this, as well as other forms of experimental hypertension, there appears to be an inverse relationship between blood pressure and serum dopamine-β-hydroxylase. Preliminary studies in Man, using plasma obtained from donors to the NIH blood bank, appears to support this inverse relationship between blood pressure and levels of this enzyme.

Dr. Andre Dubois has shown that the inhibition of gastromotility responsible for postoperative paralytic ileus is mediated by adrenergic discharge and can be prevented by bretylium, a drug which blocks release of catecholamines. With Dr. Jacobowitz, he has demonstrated that it is the sympathetic neurones to the smooth muscle which are effected selectively.

Last year Dr. David Henry developed an extremely sensitive isotopic-enzymatic assay for catecholamines which has been applied to the study of levels of these amines in small areas of brain, particularly in the hypothalamus. Dr. J. Stephen Kizer has found that release of peptides which control prolactin release from the pituitary is dependent upon dopamine. The control by dopamine of prolactin inhibitory factor appears to be indirect and mediated by a cholinergic or other non-catechol neurotransmitter.

The release of catecholamines from nerve endings appears to be the result of exocytosis. Dopamine-β-hydroxylase is a useful index

of exocytosis. Drs. Wooten and Thoa have shown that catecholamines released by tyramine is not the result of exocytosis while that produced by nerve stimulation or other means of depolorization is exocytotic and calcium-dependent. In perfused adrenal glands, peroxidase, a large protein enzyme which can easily be localized by electron microscopy, has been shown to be taken up in adrenal medullary vesicles during exocytotic release. These studies, by Dr. John Costa, James Thomas, and N. B. Thoa, establish the continuity of intravesicular and extracellular space during discharge of catecholamines. Dr. Thomas has purified DBH and produced antibodies to the enzyme in goats. Studies on the inhibition of DBH by its antibody suggest that the enzyme, which is localized in the membrane of adrenal vesicles, as well as in the soluble contents of the vesicles, can act on the outside of the membrane. This could result in β-hydroxylation of dopamine without transport to the inside of the vesicle.

Scorpion venom has been shown by Jonathan Moss to contain a toxin which causes release of catecholamines from sympathetic nerve endings by a calcium-dependent exocytotic mechanism. The action of this toxin, which is a major component of the venom, is blocked by imipramine and by tetrodotoxin. The properties of the purified toxin are being defined and it may prove useful in isolation of specific protein constituent of the membrane of sympathetic nerves.

Studies in which adrenergic tissues are maintained in organ culture have complemented studies of control of enzymes in vivo. Drs. Webb and Berv have shown that depolorization results in increased enzyme levels, possibly by release of catecholamines and activation of adenyl cyclase which results in elevation of levels of cyclic AMP. In culture, axons sprout from the neurones of the superior cervical ganglia and grow into tissues, such as iris and pineal glands, which are innervated by sympathetic nerves. Drs. Silberstein and his co-workers showed that this growth was not species specific. The characteristics of the axonal sprouts resemble those of sympathetic nerve endings in their uptake and release of catecholamines. In vitro, studies in which pituitaries are incubated with small fragments of specific hypothalamic nuclei have been found by Drs. Kizer and Palkovits to release hormones and using this technique the distribution and control of pituitary hormone releasing factors are being examined.

Dr. Ingeborg Hanbauer has studied the effects of vinblastine on the catecholamine content and catecholamine synthesizing enzymes in the adrenal glands and sympathetic nerves. Initially, vinblastine, which combines with neurotubular protein, diminishes turnover of the catecholamine at the nerve endings, and after a delay of 2 hours the nerve endings are destroyed. The mechanism of this delayed nerve ending destruction may involve accumulation of the drug at the nerve endings as a result of axonal transport of the drug.

Section on Experimental Therapeutics
Thomas N. Chase, M.D., Chief

The Section seeks to develop by rational means improved pharmacologic treatments for neuropsychiatric disease. Most experimental efforts continue to focus on neurohumoral mechanisms, since substances participating in this process appear to act as sensitive indicators of central nervous system function and constitute the site of action of many drugs which influence psychomotor behavior. Although attempts to relate specific motor or behavioral functions to events occurring in neuronal systems in which monoamines are believed to act as neurotransmitters still command most of the Section's resources, new techniques have been developed during the past year which promise to extend our capabilities to examine closely related systems in which acetylcholine, γ-aminobutyric acid (GABA) or the prostaglandins may serve as neurohumoral agents.

Since the satisfactory demonstration of neuronal histofluorescent is dependent upon the freeze-drying of tissues soon as death, it has not, heretofore, been practical to apply this method to human post mortem specimens. Work conducted with Drs. S. Balch and D. Jacobowitz now indicates that incubation in an oxygenated, physiologic medium can restore neuronal fluorescence to dopamine-containing terminals in rat cerebral tissues maintained *in situ* for as long as 8 hours after death. Preliminary applications of this technique to human autopsy material suggest that it may now be possible to study the distribution of monoaminergic systems in man's brain and search for possible abnormalities in patients with such diseases as parkinsonism and schizophrenia.

Although abnormalities in monoamine-containing neuronal systems have been implicated in the pathogenesis of disorders of affective state and extrapyramidal function, the role of parallel neuronal pathways, especially those in which acetylcholine may serve as a neurotransmitter, have yet to be carefully explored. An isotopic tracer technique has now been developed with Drs. G. Glaubiger and R. Matta which enables *in vivo* studies of the central acetylcholine metabolism. Pharmacologic agents such a 5-hydroxtryptophan and parachlorophenylalanine believed to act relatively specifically on serotonergic function, were found to modify significantly acetylcholine turnover. Lithium, which has been thought to ameliorate bipolar affective states by influencing noradrengic transmission, substantially inhibited choline uptake in the central nervous tissues and diminish acetylcholine synthesis. Reserpine, on the other hand, significantly accelerated the formation of this suspected neurotransmitter.

Some doubt has been expressed that lumbar CSF levels of 5-hydroxyindoleacetic acid, the principle metabolite of serotonin, can accurately reflect brain serotonin metabolism since serotonergic terminals occur in the spinal cord as well as brain. A recent study

in cats perfused through the spinal subarachnoid space with radioactively labeled 5-hydroxyindoleacetic acid conducted with Drs. R. Weir and I. J. Kopin indicates, however, that as much as 50% of the lumbar CSF content of 5-HIAA derives from cerebral rather than spinal cord metabolism.

The probenecid loading technique continues to provide important new information relevant to the dynamic state of cerebral monoamines. Haloperidol, which is believed to block dopamine receptors, substantially increased central dopamine turnover as estimated by the probenecid technique while ET 495, a suspected dopamine receptor agonist, exerted the opposite effect. These observations indicate that a causal relation may exist in man between the activity of postsynaptic dopaminergic receptors and dopamine turnover in the presynaptic neuron. They also suggest that putative dopamine receptor agonists and antagonists may provide a means for evaluating mechanisms which regulate dopamine synthesis and release in patients with nervous system diseases. Initial results in patients with Parkinson's disease, indicate that haloperidol produces little or no rise in dopamine turnover, presumably owing to the degeneration of dopaminergic neurons which attends this disorder. In Huntington's chorea patients, however, there was a marked increase in the probenecid-induced accumulation in homovanillic acid during haloperidol treatment. The diminished dopamine turnover in untreated patients with Huntington's disease may thus reflect a functional inhibition of dopaminergic neurons in response to the degeneration of striatal cells which receive their axonal terminals.

Evidence that the brittle "on-off" response of parkinsonian patients to orally administered L-dopa reflects variations in circulating levels of the amino acid rather than drug-induced changes in central dopaminergic mechanisms derive from ongoing studies conducted by Drs. A. Woods and G. Glaubiger. For each patient rates of intravenously infused L-dopa could be found which maintained plasma L-dopa levels constant and the patients in a stable clinical state. These observations have now prompted clinical trials of sustained release preparations of L-dopa. Preliminary results of a double-blind, cross-over study conducted in parkinsonian patients with Dr. J. Fermaglich indicate that at appropriate dose levels methyldopa, a regularly marketed antihypertensive agent, is as effective a potentiator of L-dopa as the experimental compound, α-methyldopahydrazine. Moreover, the ability of either agent to overcome L-dopa induced adverse effects was indistinguishable. Although these findings may be attributable to a partial barrier to the entry of methyldopa into the central nervous system, they would appear to cast doubt upon the commonly accepted mechanisms by which peripheral decarboxylase inhibitors potentiate the antiparkinsonian action of L-dopa.

Attempts to modify central nervous system function with the newly developed pharmacologic agents continue. The anti-parkinsonian

efficacy of ET 495, a suspected dopamine receptor agonist, has now been studied in 6 patients. Despite the marked changes in central dopamine metabolism already described, only mild symptomatic relief occurred. On the basis of recent observations that thyrotropin releasing hormone (TRH) potentiates the motor effects of L-dopa in mice, clinical studies of the ability of this hypothalamic tripeptide to enhance the efficacy of L-dopa have now begun in collaboration with Dr. M. Lipton. Attempts to elucidate the relationship of GABA containing neuronal systems to psychomotor function in man are now in progress using BA-34,647, a centrally active p-chlorophenyl derivative of this suspected central neuromediator.

Section on Psychiatry

Irwin J. Kopin, M.D., Acting Chief
Frederick K. Goodwin, M.D., Chief, Clinical Research Unit 4-West
Dennis L. Murphy, M.D., Chief, Clinical Research Unit 3-East

The research aims of the Section on Psychiatry continue to be based on development and application of methods for clinical evaluation of psychiatric status. Attempts are made to relate spontaneous and drug-induced changes in behavior to pharmacological actions on neurones and biochemical changes in brain amine metabolism.

The two clinical units in the Section, while functioning as cooperative and collaborative subsections, have each taken the lead in separate aspects of clinical and related fundamental investigations.

Dr. Frederick Goodwin and his associates have examined metabolites of the biogenic amines in urine and cerebrospinal fluid. The studies of CSF amine metabolites in affective illness and schizophrenia have been extended in collaboration with investigators in Boston, to include patients with cord transection and spinal fluid block; these studies have suggested that while the metabolites of serotonin and norepinephrine may arise from the spinal cord, HVA, the metabolite of dopamine, comes almost wholly from brain. The relationship between CSF amine metabolites and a large number of clinical characteristics have been examined in depressed patients. The probenecid technique for the study of amine turnover in the central nervous system of man has been applied to depressed, manic, schizoaffective, and schizophrenic subjects, and has revealed further effects of diagnosis and of psychoactive drugs on central amines. Amine metabolite accumulation in CSF after probenecid administration has been found to have some value in predicting clinical response to antidepressant drugs. Studies on the mechanism of the antidepressant action of electroconvulsive therapy (ECT) have revealed a decrease in turnover of brain serotonin in patients receiving this treatment. Experimentally induced changes in levels of physical activity have been found to produce changes in both urinary and CSF amine metabolites.

In primates a system has been developed for chronic collection of CSF from cistera magna and lumbar space simultaneously. This preparation will allow examination of the dynamics of amine metabolite transport so that the effects of drugs can be examined and the results extrapolated to Man.

Studies on blood platelets as models for aminergic mechanisms in brain have been continued by Dr. Murphy and his collaborators. Studies in twin and siblings indicate that in platelets monoamine oxidase levels are primarily a function of individual genetic differences. Psychiatric patient populations have been compared with normal controls and with patients with medical (non-psychiatric) illnesses; reduced platelet MAO levels have been found in schizophrenic individuals and, to a lesser extent, in bipolar depressed patients, while unipolar depressed patients are no different from normal.

Verbal learning measures studied in depressed patients indicate that depression is associated with diminished longer-term memory which is characterized principally by an increase in errors of omission. Spontaneous clinical improvement and improvement resulting from imipramine and lithium produced improvement in learning; L-dopa and L-tryptophan also improved learning but with these agents the memory improvement was not associated with changes in depression ratings.

Collaborative studies involving both clinical units have shown that a variety of clinical, biological and pharmacological parameters differentiate bipolar from unipolar affective illness.

In addition to clinical and genetic differences previously reported, bipolar depressed patients have been found to differ from unipolar patients in their behavioral responsivity to L-tryptophan, in the relative amounts of dopamine and its metabolites excreted after a large dose of L-dopa, and in D, MA, and SI scale scores on the MMPI. Systematic studies of ego defensive patterns in manic-depressive patients have revealed unipolar and bipolar differences as well as similar patterns of change accompanying improvement in either depression or mania.

Studies of clinical phenomenology in affective illness have revealed that depression and mania are not altogether "opposite" states and that level of psychomotor activity best differentiates the two states; distinct "stages" of the manic episode have been delineated and specific items have been found to reliably differentiate manic from schizoaffective patients.

In a double-blind, randomized-order treatment study of lithium carbonate, phenelzine and imipramine in depressed patients, initiated for comparison with studies of experimental drugs in this program, both lithium and imipramine were found to have significant antidepressant effects, while phenelzine was found

to be virtually without significant antidepressant action. Differential effects in different diagnostic subgroups have begun to emerge.

A newly revised computer-scored affective disorder rating scale has been factor analyzed and has been put into daily use.

Preliminary studies of the effects of short-term sleep deprivation have revealed that loss of a night's sleep results in a transient elevation in mood which lasts about one day.

In a review of the family histories of 53 patients with affective disorders, a significant degree of "assortative mating" has been found; subjects with a family history of affective disorders tend to select mates having a similar family incidence of this disorder.

Office of the Chief
Irwin J. Kopin, M.D., Chief

Unit on Clinical Pharmacology (Julius Axelrod, Ph.D. and Irwin J. Kopin, M.D., CoHeads). A technique has been developed by Dr. Michael Ebert for the continuous collection of cerebrospinal fluid from the cerebral ventricles of monkeys. This preparation is to be used to study amine metabolites, drug distribution in brain, and dynamics of cerebrospinal fluid flow.

Radioimmunoassay of a number of narcotic drugs (heroin, morphine, etc.) are being set up by Drs. Ebert and Gross and are planned to be used for study of distribution and metabolism of the drugs in experimental animals and Man. Drs. Ng and Hawks have developed Mass Spectroscopic methods for assay of cocaine and its major metabolites and are applying this technique to identify the fate of cocaine in experimental animals. Dr. Ng has also continued studies on the role of L-dopa in displacing serotonin as a mechanism for its toxic or therapeutic effects in parkinsonian patients.

Unit on Analytical Biochemistry (Robert W. Colburn, Ph.D., Head). Studies on synaptosomes (the pinched off nerve endings of brain) as a model for neurones in brain have continued. With Mr. Jonathan Moss, it has been shown that scorpion venom induces release of amines from these particles and that this release is calcium-dependent. With Dr. Larry Ng, the synaptosomes were found to contain the highest concentrations of drugs, such as Δ^9THC, diphenylhydantoin, etc. and that these drugs affect the ability of synaptosomes to take up and retain norepinephrine. Further studies on the role of metal ions in complexing and binding neurotransmitters in the nerve endings have suggested that phospholipids as well as ATP may be involved in the binding mechanism.

Unit on Clinical Biochemistry (Edna K. Gordon). The primary concern of the Unit of Clinical Biochemistry has been in studies attempting to correlate biochemical and behavioral changes in humans. Thus a major portion of the work has been in collaboration with the Section on Psychiatry, contribution of this unit in relating to the biochemical determinations in these studies.

The major brain metabolite of norepinephrine has been previously shown by this and other laboratories to be 3-methoxy-4-hydroxyphenylglycol. Last year this unit was able to develop a sensitive and specific method for assay of this compound. We have found lower concentrations of MHPG in the cerebrospinal fluid (CSF) of depressed patients than in that of other patient groups. In addition to supporting this observation, this work has been extended to study the effects of exercise and drugs in this major metabolite of norepinephrine.

The unit on Clinical Biochemistry is also concerned with gaining knowledge of the mechanism of transport of norepinephrine and its metabolites from brain, to examine the validity of the assumption that lumbar CSF reflects brain metabolism of norepinephrine. Both the Section of Experimental Therapeutics and the Section of Psychiatry treat patients with probenicid to study the accumulation of acid metabolites of dopamine and serotonin after blockage of transport by the drug. Portions of the lumbar CSF collected for these studies were analyzed for the neutral MHPG and its acidic sulfate. A small but significant increase was found in free MHPG but not in its sulfate. These observations suggest that norepinephrine metabolites may not be transported out of the brain by the same transport system as homovanillic acid and 5-hydroxyindoleacetic acid.

Methods are being developed to enable more accurate and sensitive measurement of MHPG, vanillyl mandelic (VMA) and other amine metabolites in brain, blood and cerebrospinal fluid. These methods are essential to further clinical studies on the rate of amine metabolism in brain and to test in animals assumptions regarding methods of assessment of amine turnover in human brain.

Unit on Histopharmacology (David M. Jacobowitz, Head). The Unit on Histopharmacology (Office of the Chief) is involved in histochemical, biochemical and behavioral studies in animals treated with neurotoxic agents such as 6-hydroxydopa, which selectively destroys a portion of the noradrenergic nerves in the central and peripheral nervous system. Correlation of "emotionality" with norepinephrine in various brain regions leads to the conclusion that brain norepinephrine in the telecephalon and/or hindbrain is an inhibitory component of emotional arousal. Studies with 6-hydroxydopa in shock-induced aggression is modulated through a central noradrenergic system. Fluorescent histochemical

studies of monoaminergic nerves in the brain show both degeneration and regeneration (sprouting of noradrenergic nerves), thereby demonstrating the ability of active growth of monoaminergic nerves in the adult brain.

Mapping of noradrenergic pathways in the brain has revealed new tracts to the hypothalamus, thalamus, amygdala, hippocampus, septal area and cortex.

Another major activity of this unit involves the study of nerve growth in organ and dissociated cell cultures. It has been demonstrated that ganglia from one species can reinnervate the iris of another species. It was also shown that explants of the substantia nigra region of the newborn rat brain survive for up to six days and are capable of growth of dopaminergic nerve terminals. Dissociated chromaffin cells from sympathetic fetal ganglia have the ability to produce extensive ramifications of varicose terminal catecholamine-containing processes. It is believed that chromaffin cells may play an active role in ganglionic function. Studies of various clones of mouse neuroblastoma cells have revealed a few clones with scattered intense fluorescent catecholamine-containing cells, thereby demonstrating the potential capability of these cells to differentiate.

Degeneration and regeneration is being studied in vivo in peripheral nerves by the use of vinblastine, a drug which has been shown to inhibit axoplasmic flow. Vinblastine placed directly on the superior cervical ganglion causes degeneration of both the postganglionic sympathetic trunks and the preganglionic cholinergic nerve endings. This initiates an enormous response of sprouting of catecholamine-containing terminals in the ganglion. Thus, catecholamine terminals emanate from adrenergic neurons and/or chromaffin cells within the ganglion. The mechanism that initiates sprouting of new nerves is a problem of major interest to this unit.

Since vinblastine was demonstrated to destroy cholinergic preganglionic nerves, it was of interest to use it as a tool to destroy cholinergic (vagal) nerves in the dog heart. This study has led to the observation that there is a rich network of cholinergic nerves intimately related to Purkinje fibers in the ventricular septum and that stimulation of the vagus nerve decreases vulnerability of the ventricle to current-produced fibrillation.

Annual Report of the Laboratory of Clincal Psychobiology

National Institute of Mental Health

Frederick Snyder, M. D., Chief
Robert A. Cohen, M. D., Ph.D., Acting Chief

July 1, 1972 through June 30, 1973

In last year's annual report, Dr. Snyder noted his hope that "while he chases giraffes through the thorn bush the small remainder of the Laboratory of Clinical Psychobiology staff will... continue their diligent labours in Bethesda." The research program of the Laboratory has indeed continued to progress during the past year while Dr. Snyder has been on a foreign work assignment in Kenya, Africa where, in addition to teaching in the local medical school, he is collecting sleep-waking patterns from a variety of that continent's very special animals by long-range telemetry.

Section on Clinical Studies

Bernard L. Frankel, M. D., Acting Chief

The shift of direction away from the extensive longitudinal sleep studies of severely disturbed psychiatric inpatients, noted in last year's report, has continued, although the analysis of all the data from those studies is not yet completed. Instead, studies on various aspects of sleep in normal subjects and in patients with medical and sleep-related disorders have continued in collaboration with other units of the NIMH intramural and extramural programs, NIH, and other organizations.

One such collaborative venture has involved Drs. Richard J. Wyatt and J. Christian Gillin (two of our alumni now establishing an independent sleep research facility in the Laboratory of Clinical Psychopharmacology, St. Elizabeth's Hospital), through whose efforts we have continued the biochemical and pharmacological studies of sleep, examining more closely the effects of the serotonergic and adrenergic neurotransmitter systems of the brain. Because previous studies of patients with narcolepsy had demonstrated that the REM-sleep suppressive effects of monoamine oxidase inhibiting drugs were related to the alleviation of clinical symptomatology, these patients were again studied with several protocols in the effort to differentiate between effects (psychological and physiological) of the two neurotransmitter systems. A full analysis of the data is yet to be done as these attempts to unravel the biochemistry of sleep go on. The potential clinical applicability of such studies is extremely significant as part of the overall effort to extend our understanding of mental illness.

Another continuing collaboration is with Dr. Robert Coursey of the Department of Psychology, University of Maryland, who has been studying some aspects of the psychophysiological make-up of chronic primary insomniacs and is becoming more involved in the administration and evaluation of experimental therapeutic trials of biofeedback training and autogenic therapy in this disorder. Dr. Kenneth Gaarder, a private psychiatrist with strong research interests in psychophysiology, has joined Drs. Coursey and Frankel in these studies of new, non-pharmacological therapeutic approaches to insomnia, which may ultimately lead to curbing the excessive use of hypnotic and sedative drugs in these patients. We were able to demonstrate that one such approach, cerebral electrotherapy (or CET, a somatic therapy used extensively in the Soviet bloc countries) was not helpful to these insomniac patients, and found that some domestic electronics companies marketing CET machines were making unwarranted claims of CET's clinical effectiveness in their promotional literature.

In the effort to alleviate these patients' difficulties, we have been able to learn more about the psychology and sleep patterns of some of the millions who, complaining only of an inability to sleep, call themselves insomniacs. Compared to age- and sex-matched "good sleepers" with similar levels of education and intelligence, insomniacs are more high-strung, depressed, hypochondriacal, histrionic, and pessimistic. Their sleep, as recorded in the laboratory, is delayed, abbreviated, interrupted by numerous awakenings, and deficient in slow-wave or delta sleep (the stage of sleep that is felt to be most physically restorative). Although the degree of impairment of the sleep of insomniacs is not as great as expected from their compaints, on the whole there is a reasonable level of correlation between them. The important question of whether the psychological disturbances cause the sleep problems or vice versa has not been answered. We are pursuing it and other answers with the collaboration of Drs. Theodore Zahn and Carmi Schooler (of the Laboratories of Psychology and Socio-Environmental Studies respectively) who are administering a battery of tests of psychophysiological and perceptual function to the insomniacs.

In addition to the above studies, other investigations have been focusing on the effects of stress on sleep. The stress of impending open-heart surgery and the immediate post-operative period is being studied by Miss Evelyn L . Elwell, of Catholic University, Department of Nursing, who is undertaking a doctoral project with us. We are very grateful for the cooperation of Dr. Andrew G. Morrow, Chief of NHLI Surgery, in our carrying out these studies of the changes in sleep patterns prior to and following open-heart surgery. Results of preliminary data may possibly lead to suggestions of modifications in the timing of nursing procedures so as to minimize the patients' sleep loss.

The effects of the more hormonally and psychologically stressful phases of the menstrual cycle on sleep is yet another approach in researching the relationships between stress and sleep. Miss Rona Buchbinder, of our section, has been persevering in her efforts to overcome the numerous obstacles in the way of successfully collecting the sleep recordings of healthy, non-pill taking young women with regular menstrual cycles who are willing to sleep for 35-40 consecutive nights in the laboratory. This study, like the others, promises to contribute a significant building block in the construction of our understanding of sleep, the quintessential psychophysiological phenomenon.

Section on Comparative Studies
Thomas C. Douthitt, Ph. D., Acting Chief

The description of differences in patterns of sleep and waking in a variety of mammalian species as a means of discerning evolutionary trends which may in part provide an answer to the problem of the biological enigma of sleep itself has occupied the time and talent of this laboratory of the past several years. Our subjects have been wild animals captured in their natural surroundings and brought here to be studied under conditions of captivity. We have attempted to provide them with spacious living enclosures during the period of our recordings. We have utilized the latest developments in miniature implantable telemetry devices to transmit the necessary physiological information with only minimal restriction upon and interference with the behavior of the animals. With the cooperation of the National Zoological Park we have set up an outdoor enclosure for telemetric recording of the native marsupial, the Virginia oppossum, and we have studied domesticated ungulates living in their natural setting at the NIH farm in Poolesville, Maryland. But it is only now that the technical developments of our work are being utilized in a way which realizes the true objective of making a comparative study of sleep.

The field studies currently being carried out in Kenya by the Chief of the Laboratory, Dr. Snyder, of the sleep patterns and habits of a variety of animals, representatives of a broad phylogenetic range, roaming their territories at will, promise information on evolutionary patterns of sleep which could never be obtained in a zoo or a farm or certainly not in a laboratory recording box. While providing valuable information about small primitive mammals living under controlled conditions, much of our previous work here has been a series of rehearsals for this ambitious project which is now in progress. Throughout the course of these studies and especially during the period immediately preceding the launching of the African venture the assistance and support of James Bryan and his staff in the Section on Technical Development, NIMH, have been invaluable. If the project succeeds to the extent that is hoped, the development of a reliable implantable telemetric system for transmission of EEG signals over relatively long distances will be largely responsible.

Good research strategy dictates that a balance of struck between field observation and laboratory manipulation and so investigations of factors which control the sleeping habits of several of our favorite species have continued here in addition to which we have attempted to bring up to date the scoring and analysis of a vast amount of animal sleep recording obtained previously.

Most of the animals we have studied demonstrate a very marked dependence upon light and dark changes in the environment whether they are artificially imposed in the laboratory or occur naturally as in the case of our recordings from oppossums who live outdoors at the National Zoo. One species, however, the mountain beaver (Aplodontia rufa) shows a very prominent cycling of sleep and waking with a period length of 4-6 hours which is apparently quite independent of light and dark showing nearly equal distribution of these states in both, and persisting undisturbed under both constant illumination and constant darkness. Although statistical techniques are hardly necessary for the appreciation of the phenomenon itself, we have employed the methods of auto- and cross-correlational analysis on recordings obtained simultaneously from animals living under the same conditions. These analyses have demonstrated that the animals cycle independently and thus the improbability that this ultradian cycle occurs in response to some external stimulus. We have been able to increase the frequency of the cycling by injecting thyroxin and have thus demonstrated the importance of metabolic processes among the many possible endogenous factors which could influence the behavior.

We have confirmed the reported absence of REM sleep in the echidna, the only mammal yet studied who does not show this state. By allowing a long period of adaptation to the laboratory and by using telemetry instead of conventional cable recording techniques, we have reduced the probability that this unusual situation is an artifact of life in an unnatural setting.

Our studies of hibernation carried out in the European hedgehog have demonstrated that as environmental temperature is lowered gradually, the amount of time spent awake increases. The animals which hibernated did so after a few days at 40° F. The state of hibernation was entered rather abruptly from waking and was accompanied by a sharp decline in body temperature from normal range to slightly above ambient levels.

The effects of immobilization stress upon the sleep of rats have been studied in detail by Nellie Bugbee, whose preliminary work on this problem suggested a pronounced disruption of sleep with REM suppression both during and after the period of stress. Biochemical studies of stressed animals carried out in the Laboratory of Clinical Science, NIMH, had shown effects of the procedure upon catecholamine levels and turnover persisting long after the stress was terminated. These findings, in combination with our interest in sleep as a sensitive indicator of behavioral adaptation, encouraged a detailed examination of the effect. In contrast to expectations, however, the effects of this stress upon sleep were quite negligable. Transitory disturbances occurred immediately following the two hour immobilization each day, but subsequent compensatory

changes produced fairly normal daily percentages of both REM and NREM sleep throughout and following the 28 day period of stress. Most of tha animals thus adjusted fairly well in this respect to a procedure which was obviously quite aversive for them. The importance of evaluating repeated 24 hour EEG samples in experimental studies of sleep in animals is clearly demonstrated by this surprising finding.

Several pharmacological studies have been carried out in this laboratory during the past year in collaboration with Dr. Jorge Perez-Cruet of the Laboratory of Clinical Science, NIMH, and also with Dr. Yvonne Brackbill of the Department of Obstetrics and Gynacology, Georgetown University School of Medicine. The remainder of this report will summarized the results of these studies.

Reports published recently have suggested that prostaglandins, in addition to other effects, produce a state of sedation accompanied by EEG activation which resemble in many aspects the characteristics of REM sleep. We have studied the acute effects of four of these compounds in rats and cats and have concluded that while superficially similar, the drug state and the sleep state are not identical. Our studies have indicated that the prostaglandins produce a strong cholinergic activation which persists in the central nervous system long after peripheral signs have subsided. The duration and intensity of the effect varied greatly among the four compounds tested. The most striking effects were obtained with PGE_1. Following termination of the response, apparently normal alternation of sleep and waking were resumed by both species of animals studied.

The studies on aggression in the rat pursued so productively in the laboratory during the two years of his stay here by Dr. Burr Eicheman have continued this year in the hands of Drs. Perez-Cruet and Douthitt. These studies have focused exclusively upon predatory aggression (mouse killing) in the rat, and especially upon the effects on this behavior produced by a new compound, 5-6 dihydroxytryptamine (5-6 OH,HT), which destroys serotonergic nerve terminals in the brain when injected intracerebrally. Like para-chlorophenylalanine, which inhibits synthesis of serotonin, the depletions produced by this new compound are associated with a dramatic increase in predatory aggressive behavior. An enhancement of this effect was obtained when rats treated with 5-6 OH,HT were injected concurrently with 6-hydroxydopamine (6-OHDA) intracerebrally, which destroys adrenergic terminals with consequent depletion of catecholamine levels in the brain. Since atropine sulfate blocked the killing produced by depletion of both serotonin and catecholamines in combination, but not in animals depleted only of serotonin, we concluded that adrenergic mechanisms were capable of supporting predatory aggression in animals where these mechanisms are intact, serotonin levels are lowered, and cholinergic activity is blocked.

The involvement of catecholamines in predatory aggression is further substantiated by the results of several other experiments we have conducted. We have found marked elevation in synthesis rates for both dopamine and norepinephrine in rats who are spontaneous mouse killers compared to rats of the same strain who never kill. There were no differences in monoamine levels between the two groups however. Also, alpha-adrenergic receptor blockade with dibenzyline produces a suppression of aggression in both spontaneous mouse killers and in animals treated with 5-6 OH,HT. Our current efforts attempt to more fully examine the role of catecholamines in predatory aggression, and to examine the similarity between pharmacologically-induced and spontaneous mouse killing.

The technique of biochemical serotonergic and adrenergic nerve terminal destruction with 5-6 OH,HT and 6 OHDA has also been employed in other, more strickly psychophysiological, studies. We have examined the effects on the cardiac orienting response of central or peripheral destruction of either of these systems in the rat and have found that only the peripheral damage produced in intravenous treatment with 6 OHDA blocks the typical bradycardia observed during novel non-aversive stimulation. Since intracerebrally treated groups showed no differences from the control response although brain levels of either catecholamines or serotonin were significantly lowered, it is clear that neither of these transmission systems is solely responsible for the central mediation of the response. It is further demonstrated that peripheral mediation is carried out by the adrenergic system.

Developmental changes in response patterns to stimulation during the first month of life in rat pups and the influence upon these of the concurrent maturation of central adrenergic mechanisms have been studied in collaboration with Dr. Brackbill whose studies on the behavior of the human neonate are well known. Her previous observation of a shift from suppression to elevation of arousal level in response to continuous auditory stimulation at about 10 days of age in the rat led us to investigate whether central adrenergic mechanisms were involved since brain levels of catecholamines approach adult values at about that time. The method of adrenergic nerve terminal destruction with 6 OHDA injected intracisternally 24 hours after birth was used. Our preliminary findings suggest that central adrenergic function is involved in the shift from quieting to increased activation since drug treated animals continue the neonatal pattern of response long after it has disappeared in control animals.

Annual Report of the Laboratory of Psychology

National Institute of Mental Health

David Rosenthal, Ph.D., Chief

July 1, 1972 - June 30, 1973

In FY 1973, the major goal of the Laboratory has been to maintain our past levels of research quality and productivity in the face of hiring freezes, reduced positions, and reduced operation funding. We believe that we have been fairly successful in this aspiration, but if the past trend continues, our goals and accomplishments will have to drop to lower levels in future years.

The major research areas in the Laboratory continue to include brain and behavior, schizophrenia, other adult psychopathology, minimal brain dysfunction and other childhood disorders, behavioral development, communication processes, thinking and problem solving, perception, and genetic factors in abnormal and normal subjects. The research on creativity is almost completed and will be phased out shortly. The new laboratory for the study of infant behavior is now completed and operational, and the first studies are in the process of being formulated, reviewed and soon,we hope, implemented. Our major research findings in FY 1973 are:

Brain Function and Behavior in Primates

I. Cortical Mechanisms in Vision.

A continuing collaborative study between our laboratory at NIMH and Gross's laboratory at Princeton has provided an answer to the long-standing puzzle regarding the neural basis for the participation of inferotemporal cortex in visual functions. Gross and his colleagues discovered that inferotemporal cells in the monkey have well-defined visual receptive fields, thereby establishing that the inferotemporal area received a specific visual input. Furthermore, the properties of these receptive fields (their large size, extension into the fovea and bilaterality) are consistent with an earlier conclusion derived from anatomical and ablation studies in our laboratory that the visual input to each inferotemporal area stems from the striate cortex of both hemispheres by way of the prestriate cortex and the corpus callosum (the latter being utilized in the case of the crossed inputs). Prompted by this close fit between the new data and the earlier theory, we are collaborating on an experiment to determine whether specific lesions in this hypothesized cortical pathway will produce predicted alterations in the receptive field properties of inferotemporal cells. As a first step, the property of bilaterality was selected for study. Monkeys were prepared here with either complete unilateral (left) striate removals or complete transections of the forebrain commissures, and were then studied electrophysiologically by Gross's group. The results have thus far confirmed predictions by showing that in the absence of the left striate cortex, inferotemporal

units in both hemispheres "see" only the visual field projecting to the right striate cortex (i.e., the left field for units of both inferotemporal areas); and also that in the absence of interhemispheric connections, the inferotemporal units of each hemisphere "see" only the visual field projecting to their own striate cortex (i.e., the left field in the case of right inferotemporal units, and the right field in the case of left). The neural model emerging from these results is that of a system of cortically relayed visual inputs converging onto single units in the inferotemporal area. Additional lesions have now been made in order to test this model in greater detail. For example, the splenium of the corpus callosum and the anterior commissure have been transected separately in order to determine whether only one of these pathways or both are responsible for the crossed inputs.

In the normal animal, approximately 2/3 of the inferotemporal units that are responsive to visual inputs have bilateral receptive fields (as compared to none with bilateral fields in the unilaterally destriated or totally commissurotomized animal). An interesting possibility is that it is these bilateral units which account for the equivalence of stimuli in the left and right visual fields, an equivalence that is reflected for example in the spontaneous interocular transfer of a visual discrimination habit in the chiasm-sectioned (but otherwise intact) monkey. This hypothesis might be examined by sectioning the optic chiasm in infant animals and rearing them with the two fields (i.e., eyes) occluded alternately in the attempt to preserve vision in both fields, and yet eliminate the population of units with bilateral fields. The effectiveness of this procedure in eliminating bilateral units could be tested electrophysiologically, after its effectiveness in eliminating interocular transfer had been tested behaviorally. Absence of both interocular transfer and unit bilaterality, despite the presence of the forebrain commissures, would provide strong evidence that the phenomenon of stimulus equivalence depends on convergence of inputs at the level of single units.

The evidence cited above in support of a transcortical pathway from striate through prestriate to inferotemporal cortex favors a sequential activation model for object vision. This raises the question of whether or not such a model can be extended beyond the visual system to encompass stimulus-reward associative learning. Translated into functional anatomical terms the question is whether visual objects might gain motivational and emotional significance through an interaction between the inferotemporal cortex and the limbic system. The three major telencephalic outputs from the inferotemporal area are (a) to the orbital frontal cortex, (b) to the temporal pole and amygdala, and (c) to the fusiform-hippocampal gyrus and hippocampus. As a start toward investigating the possible role of these inferotemporal-limbic pathways in visual associative learning, three groups of animals, each with damage to a different one of the three limbic structures, were compared with operated and unoperated controls in object reversal learning. This task was chosen because of its presumed sensitivity to associative learning processes. The results indicated that whereas the hippocampus, and by implication, pathway (c), is probably not involved in visual associative learning, both of the other limbic structures, and by implication, both of the other pathways, are intimately involved. Furthermore, these two pathways (a and b) probably serve different functions in visual learning, since the two lesions (orbital frontal

and temporal pole plus amygdala) yielded a double dissociation of deficits. Specifically, the frontal group was more impaired in suppressing or abandoning old stimulus-reward associations, while the temporal group was more impaired in establishing new ones.

To determine directly whether the temporal pole and amygdala are involved in the establishment of stimulus-reward associations, the activity of single units in these areas will be measured while an animal performs a visual discrimination task. Two grossly dissimilar stimuli, A and B, will be presented in random succession, and the animal will be trained first with A the rewarded stimulus in the pair, then with B the rewarded stimulus, and so on through a series of discrimination reversals. Positive evidence for our hypothesis would be provided by a finding that the discharge frequency of a given unit depends on the reward value of the stimulus (A+ vs A-) and not on its sensory quality (A vs B). The converse results, i.e., sensitivity to the sensory and not to the affective quality of the stimulus, would be expected of units in the inferotemporal area, for according to the present model this tissue is an intrinsic part of the visual system.

The view that the inferotemporal cortex belongs to the visual as opposed to an associative learning system still leaves undefined its specific role in vision. One possibility currently being examined is that this area, particularly its rostral part, contributes to visual memory by providing the circuitry that preserves short-term traces of recent inputs. Such a view is consistent not only with the available evidence from ablation studies, but also with the "protected" position of the area two or more synapses removed from the striate cortex which, by contrast, must reflect faithfully the input of the moment. To test the notion, the effects of anterior inferotemporal and other temporal-lobe lesions are being compared on delayed matching-from-sample (DMS) problems. Preliminary work on normal animals has revealed a powerful proactive interference effect in the traditional DMS paradigm, together with a simple method for eliminating it, viz, presenting new objects on successive trials instead of the same objects. Both versions of the task are being utilized in the attempt to identify the source of any visual memory defect discovered in the operated animals.

II. Frontal Cortical Mechanisms in Spatially Directed Responding.

The functions of the frontal lobe, particularly those mediated by that large expanse of cortical tissue anterior to motor cortex, remain as elusive as they are intriguing. Unlike the posterior association cortex, which appears to be linked to visual, auditory, or somatosensory sensation, the prefrontal association cortex is panmodal, and deficits arising after injury to this area are functionally complex. This laboratory has attempted over the years to specify more precisely both the nature of the impairments following frontal injury and the neural substrates responsible for these impairments. The rhesus monkey has been a favorite subject for these investigations because its brain is organized similarly to that of man, and because injury to the prefrontal cortex in monkey results in reliable selective and for the most part irrecoverable losses in the ability to perform certain tests (e.g., spatial delayed-response). Analysis of the delayed-response and related deficits should provide a clue to the function and perhaps also to the

mechanisms residing in this large and evolutionarily significant region of the primate brain.

In spite of the complex afferent input to the prefrontal area, current conceptions about the functions of the prefrontal area have been cast in modality-specific, sensory-analytic terms. The fact that the classical delayed-response tasks generally lack salient exteroceptive cues to guide spatial orientation has led many investigators to conclude that proprioceptive cues are involved in solving such tasks and hence that proprioception is disrupted by frontal lesions. Such a view, it should be noted, regards the prefrontal cortex as a final station in the processing of proprioceptive sensation much as the inferotemporal region is in the processing of visual information. Another way to conceptualize the frontal disorder, however, is in terms of a form of spatial agnosia which is not reducible to a defect in sensation. Experiments completed this year bear on the relative merits of these alternative views. Monkeys with dorsolateral prefrontal lesions and unoperated controls were trained on a spatial reversal task in such way as to allow them to base their learning either on proprioception or on orientation to a distinct place in the environment by developing a "cognitive" map of the spatial location. The monkeys with prefrontal lesions performed as well as the controls when the reversal learning was based upon proprioception but were impaired when the learning involved orientation to external landmarks in the environment. These results indicate that spatial learning impairments in monkeys with dorsolateral prefrontal lesions are not due simply to a defect in proprioceptive sensation, but involve instead a difficulty in the development or retention of cognitive spatial maps. This study is part of a series of investigations designed to elucidate the functions of the dorsolateral prefrontal region of the frontal lobe. Taken together, they have dispelled the prevalent view of a unitary dorsolateral function by demonstrating that the functions of the cortex in the arcuate region are dissociable from those in the region of the principal sulcus; they have established that the function of the cortex in the principal sulcus involves a highly specific form of memory disturbance; and, finally, they have provided evidence that the nature of this memory disturbance involves short-term memories for the organization of the visual-spatial world, rather than a defect in learning based upon proprioceptive sensation.

While a great deal is known about the functions and anatomical connections of the prefrontal cortex, almost nothing is known about the neurochemical properties of this region. Do the anatomical pathways to and from the prefrontal cortex involve selective neurochemical transmitters? Can the major functional subdivisions of the prefrontal cortex be differentiated in terms of different neurochemical pathways? Does injury to the prefrontal cortex result in disturbance in metabolic functions in regions remote to the injury, for example the caudate nucleus or the hypothalamus? If so, are these effects slighter if the injury is sustained in infancy or in stages (e.g., serial lesion phenomenon). These and other questions are concerned with elucidating the relationship between the physiology, anatomy, and biochemistry of the neural substrates of behavior. Much is known about each of these properties of neural tissue separately but little attempt has been made to relate each to the other. This year the Section on Neuropsychology and the Laboratory of Clinical Sciences have begun to explore these questions collaboratively.

An initial investigation is in progress on the effects of dorsolateral and orbital prefrontal lesions on the metabolism of biogenic amines in various regions of the central nervous system. Preliminary results suggest that these lesions produce widespread metabolic effects and that an important and fruitful line of investigation has been opened.

III. Cerebral Mechanisms For Functional Recovery After Brain Injury.

The study of the cerebral cortex in the adult monkey is intriguing because its removal produces selective, reliable, and on some tests, irrecoverable behavioral impairments. The investigation of cortex in the infant monkey, by contrast, interests us precisely because its removal fails to result in such deficits. The difference between the study of lesions in the infant and in the adult is more than one of the dissimilarity of outcome, however, for the two types of investigations pose quite different problems. Whereas the essential question confronting the investigator of cortical function in the adult is the nature of processes intrinsic to the damaged substrate, the task confronting the student of the early brain-injured is the understanding of the capacities of residual areas, since presumably these are the areas responsible for sustaining the functions of the cortex which has been removed. Thus, our investigations are concerned with identifying the neural substrates which mediate behavioral recovery in young brain-damaged animals.

In the basis of studies involving selective lesions of the prefrontal cortex in infancy we have been able to identify two expressly different patterns of recovery. We found that monkeys given orbital lesions in infancy were initially as impaired as monkeys given the same lesions as adults but that later in development the early-operated monkeys gave evidence of dramatic recovery. By contrast, monkeys given dorsolateral lesions as infants were initially unimpaired but later in life this picture of normality gave way to one of retarded development. On the basis of such results we have proposed that there is a central principle governing whether or not recovery will occur, approximately when it will occur, and whether it will follow the progressive or regressive pattern. The principle concerns the maturational status of functionally related areas that remain undamaged by the early brain injury. If there remains undamaged a related area which is relatively "uncommitted" to its own course of development at the time of brain injury, then recovery will ensue. If, on the other hand, the surviving tissue is already "committed" or relatively mature, then presumably it will have lost this capacity for reorganization, and hence will be unable to take on new functions. Regarding the prefrontal cortical areas, the available evidence suggests that the orbital cortex becomes "committed" considerably earlier in ontogeny than does the dorsolateral area. Thus, it seems reasonable to suppose that in monkeys given orbital lesions in infancy, the remaining dorsolateral cortex could come to assume the functions of the orbital cortex but that the orbital region could not reciprocate for damage to the dorsolateral cortex. The full expression of compensatory readjustment would be delayed, of course, until the compensatory structure itself attained functional maturity. Thus, the finding that dorsolateral lesions do not produce serious impairments in monkeys until they reach two years of age, together with the fact that only monkeys given orbital lesions as infants show recovery at the two-year stage provide strong evidence for this view.

Further evidence for this view comes from studies of the status of subcortical structures during development. It is well established that the prefrontal cortex is anatomically and functionally related to the caudate nucleus. The dorsolateral cortex, for example, projects to the anterodorsal sector of the head of the caudate nucleus. It is of interest, therefore, that lesions placed in this part of the caudate in infants produces serious impairments on just those tasks and at just those ages when dorsolateral cortical lesions do not. We interpret this finding to mean that the caudate nucleus becomes functionally mature earlier in development than the dorsolateral cortex and that it is capable of mediating many of the behaviors that the dorsolateral cortex will ultimately assume. According to this view, the caudate does not "take over" the functions in a compensatory sense but is at early ages, the structure primarily responsible for carrying out these functions. In the course of development, these functions become "encephalized", so to speak, with the maturation of the cortex and the caudate then loses its functional autonomy. The differential importance of the cortex and the caudate nucleus at different stages of development is dramatically illustrated by the finding that at early stages of development, lesions of the caudate nucleus produce more severe deficits than do lesions of the cortex, while at maturity, conversely, lesions of the cortex produce more severe impairments than lesions of the caudate.

Another line of evidence has been developed to support the view that the maturational status of tissue that survives injury plays a critical role in determining whether functions will be recovered. Until recently, it has been tacitly assumed that recovery of function following perinatal injury would occur to the extent that the area removed was functionally immature. Results of experiments completed this year clarify the relationship between age-at-injury and the probability of recovery. Recovery of function is greater the earlier the age-at-surgery, not because an area is removed prior to its own development, but rather because it is removed prior to the maturation of areas which survive injury. Thus, monkeys given orbital prefrontal lesions within the first, fourth or eighth weeks of life were equally impaired at the one-year stage of development, irrespective of age-at-surgery, and showed recovery at the two-year stage of development, again irrespective of age-at-surgery. The recovery at 2 years of age is attributed to the maturation of compensatory structures during the second year of life, and cannot be explained in terms of the immaturity of the region ablated.

Several other studies of recovery of function following early brain injury are in progress. One is an investigation of the effects of early prefrontal injury at still later stages of development, beginning initially when the early-operated monkeys are two years of age and continuing until they are into their fourth year of life. This study which constitutes a replication of earlier findings under more stringent conditions, bears on the possible role of experience in previous studies on facilitation of recovery, and will help to clarify whether dorsolateral lesions simply arrest development or lead to deterioration with age, over a longitudinally extended period of observation. Another study involves the opposite maneuver, constricting the period of testing into the first six months of life. Both studies are direct tests of different aspects of the developmental explanation of behavioral plasticity in early-brain damaged cases. A third study, also of theoretical importance,

involves the removal of areas thought to be involved in recovery of orbital function, once early-operated monkeys have demonstrated behavioral recovery. All studies are in progress and completion is not anticipated for several years.

Concomitant with the neurobehavioral experiments described above, we are conducting experiments aimed at elucidating the neuroanatomical basis of plasticity. Two types of neuroanatomical questions have arisen in the context of the developmental research. The first has to do with the normal development of the nervous system. We are seeking to determine when in ontogeny the dorsolateral and orbital prefrontal cortical areas establish connections with subcortical structures like the caudate nucleus. Monkeys that have received selective unilateral cortical ablations at various stages of development (2 months, 6 months, 24 months) have been sacrificed and their brains processed with silver impregnation techniques to determine the status of cortical-subcortical pathways at the different stages of development. The information from such studies will be valuable in their own right since little is known about the structural development of cortical-subcortical connections, but they will also bear directly on the hypothesis derived from behavioral research that the orbital cortex develops earlier in ontogeny than does the dorsolateral cortex. The second major question which we wish to approach anatomically concerns the presumptive reorganization of the nervous system consequent to early injury. To this end, monkeys that have been given bilateral orbital prefrontal lesions as infants, for example, will be allowed to mature and behavioral data will be collected at maturity to insure that functional recovery has occurred. At this time, unilateral cortical lesions will be placed in areas suspected of mediating the recovery and silver impregnation techniques will be employed to determine if there has been any alteration or elaboration of intact pathways (collateral sprouting) that could mediate the behavioral recovery. Ultimately, we would like to combine neurobehavioral, neuroanatomical, neurochemical, and electrophysiological approaches to obtain as complete a picture as possible of the normal development of the brain and its decreasing potential with age for neurobehavioral plasticity.

Finally, a new area of investigation has been entered upon this year relating to the prefrontal questions specifically, and to developmental plasticity, in general. This area of investigation, carried out in collaboration with investigators at Bionetics and I.B.R., involves surgical manipulation of the primate fetus. So far, one rhesus monkey fetus given a dorsolateral prefrontal lesion at 100 days of gestation, has been replaced *in utero* and delivered successfully at term (168 days of age) by cesarean section. Another case is expected to be successfully delivered in the near future. Again, this is a long-term study with critical results not expected in the immediate future. However, it is encouraging to note that the first subject is a healthy animal, with no apparent sensory or motor defects and cannot be differentiated from other young monkeys in this laboratory on the basis of unlearned behavior.

These studies have been profitable from several points of view. First, they have provided a new line of evidence to support the theory that there are two functionally distinct subdivisions of the prefrontal cortex. Secondly, they provide some clues as to the limiting factors (e.g., age at surgery, age at testing, locus of injury, maturity of intact regions) and hence to the mechanisms underlying recovery of function in developing organisms.

Thirdly, they indicate something about the normal course of brain development, a subject about which little is known. Finally, these investigations have bridged a gap previously existing between animal studies and the clinical literature. The present results parallel the findings in man by establishing evidence for both progressive and regressive sequelae of early injury to the brain. In this kind of correspondence lies the hope that the outcome of investigations on nonhuman forms can ultimately be extrapolated to conditions of developmental neuropathology in man.

IV. Cortico-subcortical Mechanisms in the Regulation of Behavior.

Our earlier work had demonstrated with anatomical procedures that efferent projections of the prefrontal cortex terminate in a topographic arrangement on two sectors of the head of the caudate nucleus. We have also demonstrated in further anatomical studies that each of these sectors in the head of the caudate send fibers selectively to two different parts of the globus pallidus. It therefore became important to establish whether or not these two anatomical systems remain differentiated beyond the pallidum. Although there was some relevant earlier work suggesting that this would be the case, our data though still incomplete, indicate that the projection of the lateral part of the pallidum to the subthalamic nucleus is selective. However, the projection of the medial pallidum appears to be more disseminated in the thalamus and subthalamus than expected. It will be important to establish the reliability of this finding in further work.

Research with the aim of demonstrating the behavioral significance of the anatomical relationships between the frontal cortex and subcortical structures has been concerned principally with tidying up findings of last year. We had found that very large lesions in the hypothalamus, involving different divisions of this structure resulted in a pattern of deficits which are characteristic of damage to the orbital frontal system, while smaller selectively placed lesions, though resulting in impairments, did not yield a pattern of deficits unequivocally characteristic of one or the other frontal-lobe system. Additional animals prepared with somewhat larger lesions and tested on an extended battery of tests have not clarified the question. Indeed, the present evidence suggest that there is considerable variability in the effects of hypothalamic lesions on behavior and that more research will be required to ascertain the sources of the variability.

The medial dorsal nucleus of the thalamus is another subcortical structure related to frontal cortex by virtue of both efferent and afferent connections. It would, therefore, be expected that this nucleus would have functions similar to those of frontal cortex. However, in several studies, some of them our own, even very large lesions involving virtually all of this nucleus have not resulted in impaired performance on tests of frontal-lobe function. Our findings of last year, however, reopened the question with the demonstration that profound deficits can result from lesions in this nucleus. Our work this year has confirmed these findings, and studies in progress are designed to determine which factor is critical in producing the impairments.

V. Somatosensory Processes.

The general aim of this research is to discover in monkeys the functional significance of the components of the somatic corticopetal inflow, namely, the lemniscal and the extra-lemniscal. Electrophysiologically, lemniscal neurons are characterized by small receptive fields, place- and modality-specificity, reliable synaptic transmission, high conduction velocity, and somatotopic organization, whereas extra-lemniscal somatic afferents in general lack such characteristics. In the spinal cord, the lemniscal pathway from each body-half is made up of three tracts, all of which have as their thalamic target the contralateral ventrobasal complex (VB). However, it is thought that one of these tracts--the dorsal column--then sends an input primarily to cortical somatosensory area I (SI, or the postcentral gyrus), whereas the other two-- the spinocervical and the neospinothalamic tracts--provide the input to cortical somatosensory area II (SII, or the parietal operculum). The situation is complicated by two further facts: VB projects not only to SI and SII but also sends a light projection to the motor cortex (the precentral gyrus) and to the posterior parietal region; conversely, other thalamic nuclei than those of VB project to all these cortical regions except possibly to SI. SI is therefore the lemniscal area par excellence, SII is mainly lemniscal, whereas the motor cortex and the posterior parietal region (as well as the whole ipsilateral sensorimotor cortex) are mainly extra-lemniscal. Thus, because of the distinctive functional properties of the lemniscal and extra-lemniscal pathways and their selective cortical terminations, it is possible for ablation studies to contribute not only to localization of function, in the traditional sense, but also to the more interesting question of neural coding.

As reported in previous years, we have established that lesions of extra-lemniscal regions do in fact give rise to impairment on some, but not all sensory tests. More recently, we have shown that a sharp functional boundary exists at the bottom of the central sulcus. Performance on motor tasks, ranging from simple to complex learned sequences, are impaired in a variety of ways by lesions of the precentral gyrus, whereas scores on a battery of sensory discriminations, whether easy or difficult and seemingly regardless of the sensory dimension investigated, are not affected at all. On the other hand, the same sensory discriminations are severely affected by immediately adjacent lesions restricted to the postcentral gyrus (SI), and this deficit appears to be permanent (contrary to reports in the literature which have claimed at most slight or transient impairment after postcentral ablations; we tentatively ascribe this difference in results to the presumed failure of others to remove the focus of the lemniscal projection in the posterior bank of the central sulcus). Our findings, stated baldly in this way, seem to conform to classic neurological teaching and to support the theory that the electrophysiological properties of the lemniscal neurons provide the neural basis of refined, discriminative sensation. Likewise in apparent agreement is our finding in the past year that lesions of SII, an area which is mainly lemniscal, produce detectable deficits on sensory discrimination tasks (also contrary to previous results by others).

Nevertheless, we have obtained data which seriously limit, or even invalidate, the lemniscal theory of fine discriminative sensitivity. Last year we reported experiments showing that, under certain conditions, monkeys with SI (or of SI and SII) have little or no impairment of such sensitivity.

Thresholds to light touch, determined with a series of graded nylon filaments passively applied to the hand, showed little or no elevation; also, temperature discriminations of about 1°C., in which the hand can remain immobile after making contact with one or the other of the discriminanda, are scarcely affected. Yet monkeys with similar or even much smaller lesions, have extreme difficulty in learning to make discriminations based on "active touch" (Gibson's term). This is not to imply that these animals are paretic, or that their movements appear in any way abnormal after the recovery period, but rather to suggest that they may not make the kind of systematic exploration that results in an acquaintance with the stimulus objects that is adequate to permit consistent discrimination. Our recent finding that animals with SI lesions have considerably more difficulty in detecting small differences in roughness (which requires rubbing) than in size (which requires only a grasp) may be in accord with the suggestion made above. This view of the function of the lemniscal system (first suggested in Semmes, 1969) is beginning to gain ground with other investigators.

Although, as mentioned above, we have established the anterior boundary of the "active touch" area (the bottom of the central sulcus), the posterior boundary is still uncertain. In the past year, we have devoted a major effort to the attempt to find this boundary, if it exists. The alternative is that the function simply fades out gradually in tissue more and more distant from the central sulcus in the posterior direction. However, previous work by others suggests that the posterior parietal region has a different function from that of the postcentral gyrus, suggesting that a posterior boundary to the "active touch" area might lie in or near the intraparietal sulcus. Five groups of animals with progressively more posterior lesions, which taken together encompass the tissue starting from the surface cortex of the postcentral gyrus and extending backward to include the surface of the inferior parietal lobule, are being studied with our battery of tests (fully described in previous reports). Originally, there were three animals in each group, but it is now clear that the inter-individual variability is such that this number must be increased, perhaps to six or more. The outcome of this study should tell us whether the parietal lobe includes a second focus representative of a separate function, how this function might be characterized, and where the boundary between the different functional zones lies. We hope also to clarify further what distinctions exist between the roles of SI and SII, other than the quantitative one we have already found in the past year, since the presence of a complete somatotopic representation in each of these areas strongly suggest that a qualitative difference exists.

Schizophrenia

A study of the offspring of schizophrenics, initiated in 1971, utilizes data collected by the National Institute of Neurological Diseases and Stroke. It aims to discover characteristics in the offspring of schizophrenics which might reflect an inherited predisposition to schizophrenia. However, our first finding is that more of the offspring of schizophrenics die a fetal or neonatal death than controls, sometimes with a neurological malformation. There are various possible reasons for this finding--a genetic defect in the child, an adverse uterine influence of the schizophrenic mother, or an effect of medication. Our forthcoming studies will focus on neurological development

in the survivors among the index group.

Social Class and Schizophrenia.

Previous studies of social class and schizophrenia have demonstrated a relationship between the two but have been unable to dissect out the factors mediating the relationship. Employing the data from our Denmark studies, we have used the technique of adoption to separate the roles of genetic and environmental effects. Our findings indicate that: (1) the relationship between schizophrenia and lower social class is not clearcut in our population, (2) the tendency for schizophrenics to be of lower socioeconomic is the consequence of their "downward drift," and (3) lower class raising does not appear to provoke or induce schizophrenia. The generality of these findings is limited because of the special nature of the populations employed.

Investigation of Psychophysiological Functioning in the Adoptees Project.

As a part of our study to investigate possible phenotypic traits of the inherited predisposition for schizophrenia, we compared the results of a measure of sympathetic nervous system functioning (GSR) recorded during an orienting and conditioning procedure administered to two subject groups. The adoptive index group consisted of adult subjects who were the biological offspring of a schizophrenia parent, but who had been given up for adoption at an early age. Our comparison group were adoptive controls whose biological parents had no record of schizophrenia or a schizophrenia related illness. Groups were matched for age, sex, age of transfer to the adopting home and socioeconomic status. The groups were compared for: amplitude of response, baseline differences, frequency of response, latency of response, response recovery time, habituation of responses and conditionability. There was statistical evidence of increased amplitude of response and frequency of response for the index adoptees as compared to the controls, but these differences were not consistent across the two portions of the testing procedure (orienting and conditioning). No other measures proved to discriminate the two groups statistically.

This same procedure was administered to a group of subjects who were the offspring of a schizophrenic parent and who were reared by their biological parents. These subjects were matched to the control adoptees for age, sex and socioeconomic status. Here, we were simply looking to see if the combination of rearing by a schizophrenic parent and a genetic endowment for the disease produced discernible differences in autonomic functioning when compared to our group of adoptive controls.

The same comparisons as those made between the index adoptees and adoptive controls (with the exception of latency of response) produced only one statistically significant result. The nonadoptees produced significantly more conditioned responses than did the adoptive controls.

This finding supports, in part, the Mednick-Schulsinger theory that schizophrenia occurs in individuals who exhibit an abnormally high degree of conditionability. Our results seem to support this notion but give little support to their hypothesis that individuals predisposed to schizophrenia exhibit increased anxiety as measured by autonomic functioning procedures.

Variance Analysis of Reaction Time Data.

In addition to the adoptive index (AI), adoptive controls (AC), and nonadoptees (NA), we have as part of our study a fourth group of subjects that were selected using a modification of the cross-foster (CF) technique. Here, subjects were selected who were the offspring of nonschizophrenic parents but who were adopted by a schizophrenic adoptive parent. By combining data from these four groups in an analysis of variance design according to whether they were reared by a schizophrenic parent or not (CF, NA - AI, AC), and whether they had a biological parent with a diagnosis of schizophrenia or not (AI, NA - AC, CF), we can attempt to determine how much of the variance in performance is accounted for by rearing, by genetic endowment, and by an interaction between the two variables.

This was done with data using a simple reaction time procudure requiring either a manual or a verbal response. Subjects reared by schizophrenics produced larger reaction times than those reared by nonschizophrenic parents. This result was found consistently across the two response procedures (manual and verbal). No statistically significant differences were found between groups compared for genetic endowment for schizophrenia, and there were no significant interactions between genetic endowment and rearing.

We have found previously that chronic and acute schizophrenics do not exhibit a generalized deficit in the responsivity of the autonomic nervous system as has sometimes been thought, but show such a deficit selectively, particularly in response to meaningful stimuli and to "stressors" such as task performance. Currently, we are following up these studies by using a similar testing procedure on medication-free acute schizophrenic patients at three points in the course of their illness--soon after admission, on discharge from the Clinical Center and on a later followup. Although extensive analysis of the data has not been done as yet, it appears that the selective deficit in autonomic responsivity found previously appears only when the patients are exhibiting moderate to severe schizophrenic symptoms. When these have remitted, the patient's autonomic responsivity to all stimuli seems to increase to greater than normal levels. Tentatively, it appears as though schizophrenics, when more or less asymptomatic, have unusually labile autonomic nervous systems, but the onset of overt psychopathology is accompanied by a selective damping of autonomic response. This study will also permit assessment of the relation of changes both in autonomic function and cortical evoked potentials (AER) to changes in clinical state of the same patient as well as between-patient comparisons utilizing the intensive evaluations made by the Section on Psychiatric Assessment.

Other Psychopathology

Minimal Brain Dysfunction in Children.

Autonomic functioning and capacity for attention are being tested in minimally brain damaged children (MBD) both on and off amphetamine medication, and in normal children to assess the role of autonomic factors in the "hyperkinesis" of these children.

We have found that lithium is of no appreciable therapeutic benefit for minimally brain dysfunctioned children refractory to other forms of treatment. Preliminary findings indicate that the evoked response of MBD children differs from that of age-matched controls. MBD children appear to be "augmenters;" controls do not "augment." Furthermore, it appears that MBD children who respond to stimulant medication demonstrate diminished augmentation with such treatment whereas non-responders show increased augmentation.

Based on these clinical longitudinal studies of medication-free patients with bipolar and unipolar affective disorders, schizophrenia and 45XO chromosomes, it appears that relatively enduring mechanisms are important in determining functional stimulus-intensity relationships of the early (100-150 msec post stimulus average evoked response (AER) components; correlations with clinical behavioral ratings, or with drug effects (amphetamine, AMPT or l-dopa) are low. In contrast, later AER components (150-200 msec post stimulus) are less useful in clinically distinguishing patient groups or sex chromosome status, but are more highly related to clinical ratings and the effects of amphetamine, l-dopa and AMPT.

Psychotherapy in Creative Youths.

We have continued to study the experiences of a large group of high aptitude science students who received psychiatric treatment during college. The design of this study is unique in that the sample contains students from more than 150 colleges and universities and in that extensive data were obtained at each of three critical points in the students' lives - shortly before college entrance, after the first year of college, and one year after college. These longitudinal data make it possible to examine the evolution of the patients' difficulties and to assess the impact of current methods of psychiatric intervention on the functioning of this important subpopulation of college students. Major findings are:

(1) Approximately 2/3 of the students who subsequently received psychiatric treatment did not evidence significant emotional difficulties or problems in adjustment prior to college.

(2) Students who received psychiatric treatment tended to adapt poorly to their college environments during the first year. Loneliness, dissatisfaction with grades, and a general feeling of being "out of place" at their colleges were prominent among these students' complaints. It was noted that, in comparison to control groups, these students reported spending relatively little time working on classroom assignments and many became highly involved in artistic and literary activities.

(3) Two patterns of student-college interaction were observed: (a) Among the students who showed signs of emotional impairment prior to college, those who entered highly selective colleges (e.g., MIT, Harvard, CIT) were very likely to experience adjustment problems and to enter treatment. Those who entered less selective colleges tended not to encounter problems in adjustment, not to enter treatment, and to improve over time. (b) Most unimpaired students entered colleges with highly competitive, highly structured

academic programs and majored in science. Those who were most likely to function poorly in their college environment and to enter treatment were those who evidenced a complex of personality traits which has been found associated with high-level creative performance in adult samples - independence, assertiveness, flexibility, etc.

(4) Approximately 85% of the treatment group received some form of psychotherapy, administered by a psychiatrist or psychologist. There was essentially no evidence that this form of intervention produced an alleviation of problems or a reintegration of functioning. On the contrary, the functioning of students who received psychotherapy tended to decline over time. This decline was not confined to any one aspect of functioning, but was evident on measures of change in personality, self-perception, social and family relationships, academic performance, career development, etc. These changes were found in approximately 70% of the patients in this group. Five percent of the students who sought professional help during college received educational/vocational counseling. This was the only treatment subgroup to give evidence of beneficial treatment impact. All of the students in this group showed signs of improvement.

(5) Historically, the emphasis in college psychiatry has been on the development and staffing of programs designed to make psychotherapy available to large numbers of students. It appears that this goal has been achieved, and perhaps overachieved. It may be that too many rather than too few college students are given psychotherapy at the present time. Consideration of the predispositions, the problems, and the educational situations of the students represented in this study suggests that educational/vocational counseling was probably the treatment of choice in many cases. The findings are interpreted as indicating: (a) a need for additional longitudinal research detailing the responses of different kinds of maladjusted college students to different forms of therapeutic intervention, and (b) a need for procedures to aid college mental health workers to discriminate effectively between those students who are likely to benefit from psychotherapy and those who are more likely to respond favorably to alternative methods of intervention.

Behavioral Development

Caretaker-Infant Interchange.

One project compared, by age and environmental group, correlation coefficients between three infant and three mother (or caregiver) behavior classes during a full day of observation. Male infants and their parents/caregivers were studied at either 2, 6, or 8 months of age in four Israeli child-rearing environments: the kibbutz (collective settlement), the residential institution, and the only-child and the youngest-child urban middle-class family. The correlations were determined between the Child's visual fixation, smiling, and vocal behaviors, and the Mother's (or Caregiver's) fine contact, smiling, and talking behaviors. These correlations were grouped within caregiving settings, within purely-social settings, and between caregiving and purely-social settings. The statistically-reliable findings follow:

1. Correlation coefficients between mother and infant interaction

behaviors are more often higher in kibbutzim than in youngest-child or only-child urban middle-class families.

2. In kibbutzim, the correlations between interaction behaviors of mothers and their infants are more often higher than are those between interaction behaviors of professional caregivers (metaplot) and the same infants.

3. The correlations between interaction behaviors of kibbutz caregivers and their infants are more often higher than are those between residential institution caregivers and their infants.

4. The correlations between interaction behaviors of mothers and their infants, and of caregivers and theirs, are more often higher when the infants are 8 months old than they are when the infants are 2 months old.

In an attempt to gain insight into possible bases of these results, the magnitude patterns or intercorrelation coefficients were examined within-infant behaviors and within-mother or within-caregiver behaviors by environmental groups and by age groups. It was found that these patterns paralleled fairly closely the correlation coefficient patterns found between mother or caregiver and infant behaviors. Hence, it is prudent to emphasize the homogeneity of all magnitude patterns characterizing the in vitro correlation coefficients derived from mother/caregiver-infant interaction, whether adult-infant, infant-infant, or adult-adult. This homogeneity may simply result from the fact that all the coefficients are derived from the very same behavior-data base. In this context, it could be concluded from the product-moment correlation analysis that the interaction of kibbutz boys, and of 8-month infant boys, with their mothers or caregivers is more homogeneous than is the interaction of mother- or care-giver-infant dyads within the urban middle-class youngest child or only child family groups or within the 2-month-old group.

This higher correlation pattern characterizing interaction in the kibbutz environment, compared to those of youngest children and only children, may be due simply to the possibility that there is less of a distinction in kibbutzim between caregiving and purely-social settings. The greater number of high between-setting kibbutz correlations found would support this possibility, but the higher coefficient magnitude patterns found for kibbutz mothers than for kibbutz caregivers would not.

Contextual Determinants of Reinforcing-Stimulus Power.

The Section program includes an emphasis on the contextual determinants of stimulus power in learning. Our earlier work with children has shown that the power of a reinforcing stimulus in learning is an inverse function of their prior satiation for it, specifically of the number of times the children have been exposed to the same stimulus in a setting immediately prior to the learning task. To determine if this function holds also for highly salient stimuli provided prior to the learning task, an experiment was carried out with 50 grade-school boys. High saliency was implemented during the treatment condition by providing the stimulus word good clearly contingent on a particular response. The results showed clearly that a satiation function applies as well to stimuli of high saliency, permitting a more general conclusion about reinforcing-stimulus satiation.

Mutual Learning Implications of Mother-Infant Interaction.

We are launching our new infant-laboratory with a study of the reciprocal learning of mother and her infant, in which we shall be manipulating experimentally the interaction between mother and infant in a direct manner. In this way, we aspire to obtain leverage on the interaction process that we could not readily attain in the naturalistic investigation reported above.

Perceptual/Cognitive Development.

The general aim of the research in perceptual/cognitive development is twofold: (1) to assess the discriminative and intellective competencies of children at various ages and (2) to isolate the environmental factors which contribute to the development of these capacities. Experimentation during the past year has continued to focus on the growth of object perception and discriminative ability in the first six months of life. Of particular theoretical interest was Eleanor Gibson's thesis that perceptual discrimination of objects emerges through the progressive differentiation of their distinctive properties and structures. This "stimulus-oriented" conception is to be contrasted with various "response-oriented" theories of perceptual learning which stress the mediating role of motoric responses, either in constructing models of the external object (the Russian school) or in enhancing the distinctiveness of stimulus cues (S-R discrimination theory). It is also to be contrasted with a nativist approach, currently being revived as a consequence of the discovery of specialized receptor cells in the visual cortex for simple visual dimensions, which holds that the perception of complex events may also be built into the nervous system at birth.

The first half-year of life constitutes a critical test period for these alternative positions. Both the Russian school, which emphasizes the role of orientation movements of the hand, and the S-R conception, which stresses executive as opposed to orienting responses, would predict very poor object discrimination prior to the development of extensive manipulative activity. The nativist position, on the other hand, would predict an early and rather sudden appearance of the ability to perceive objects, particularly those which are adaptively significant for the infant. According to Gibson's model, one would expect steadily improving development in the first six months with the earliest stages exhibiting discrimination of the most salient properties of objects, followed by gradual differentiation of less prominent elements and patterns.

To shed light on some of these issues we conducted a series of experiments on perception of the human face. Previous research had yielded equivocal results regarding the infant's ability to discriminate faces. Some of the first studies with human babies had indicated that the total face is discriminable as early as 10 weeks of age, a finding generally in accord with a nativist position. More recent research, on the other hand, has found that infants are unable to detect even the eyes as late as four months of age, a datum which is at variance with Gibson's theory. One problem with all of these studies involves their use of the method of spontaneous eye fixation to determine visual preference. The failure to find a visual preference, however, does not necessarily imply a lack of discriminative ability, and the occurrence of lengthy fixations is itself ambiguous since the familiar, the discrepant, the

anomalous, and the complex are all known to sustain infant attention.

Using a variant of the habituation paradigm we examined the ability of four and five month old infants to discriminate specific elemental and structural features of the face (involving eyes, nose-mouth, hair, and contour areas). Subjects were first habituated to a distorted version of a schematic face, and, following response recovery, were shown the intact schematic face. It was expected that the more salient a particular facial attribute, the less face-like its distortion would appear to the infant, and hence the longer would be his subsequent fixation of the intact face (i.e., habituation would be less likely to generalize to the latter). The results of an initial experiment indicated that at four months of age (1) the eyes are perceptually more salient than the mouth, and are also seen as a clearly defined structure (paired in the horizontal axis and located in the upper half of the head) and (2) the head (including hair and face contour) is more prominent than the inner face configuration. A second experiment, designed to assess the legitimacy of the groups which took lengthy looks at the intact face in Experiment 1, demonstrated that their responding was indeed under discriminative control. The findings of a third experiment comparing four- and five-month-olds revealed that at five months of age the mouth has become as distinctive as the eyes, and that the total face configuration is now discriminable. The results overall support Gibson's notion that object perception develops through gradual differentiation of component features of stimuli. They suggest in addition that elemental and structural properties of objects are perceived without benefit of manipulative responses.

Genetic Studies

Genetics of Averaged Evoked Response (AER).

In order to assess the relative importance of genetic and environmental factors to AER, monozygotic and dizygotic normal twins were studied. Positive AER components at 100 and 200 milliseconds are far more alike in MZ than DZ twins; negative components have almost no heritability. Latency heritability decreased from early to late components. Drawing both on clinical studies and a series of studies of normal subjects, we find that while genetic and attentional factors are important for both early and late AER components, early components reflect a relatively fixed neurophysiological event associated with the perceived rather than the actual physical intensity of the stimulus. Later components are affected in a discrimination process, by stimulus novelty or surprise, by aging, by mood and in "attentional" disorders as in minimally brain dysfunctioned children.

Genetics and Conditioning.

Biochemical correlates of differences in conditioning in inbred strains of rats: We have found apparent biochemical correlates of strain difference. Animals who avoid with difficulty but who respond to amphetamines with increased rates of conditioning do not show abnormalities of brain monoamine metabolism, but do show decreased levels of monoamine synthesizing enzymes in the adrenal.

Studies of Normal Functioning

Perceptual Adaptation.

The visual system does not "see" the image that is projected on the retina. If it did, we would continually see the network of blood vessels lying just in front of our retinal photoreceptors. Only under special circumstances is it possible to see these blood vessels, such as when an unusually bright light is flashed into the eye. The reason is that the visual system adapts to the prevailing levels of light stimulation and is sensitive only to changes from those levels. The shadows of the blood vessels are always there in the same place on the retina, hence they do not ordinarily exist perceptually.

The phenomenon of visual light and dark adaptation has told us a great deal about how the photochemical and neural processes of the eye work. But adaptation extends to perceptual processes far beyond the simple discrimination of brightness and color differences. Form, spatial direction, motion, and many other, perhaps all, stimulus variables are subject to adaptation. It is not an exaggeration to say that our perception of reality does not directly reflect what is there in the external world but is relative to what we have adapted to.

Some years ago the discovery of specialized receptive cells in the visual cortex provided a plausible neurophysiological hypothesis for the basis of adaptational effects other than simple light and dark adaptation. Receptive cells sensitive to one orientation of a contour rather than another or sensitive to one direction of motion rather than another could account for the more complex kinds of adaptation which occur. We found in fact that adaptation to stimulus motion in one direction, while greatly altering perception of motion in that direction, did not affect perceived motion in the opposite direction. Other investigators have found that adaptation can be similarly limited to some specific combinations of motion direction and the color or form of the moving elements.

The latter results are consistent with the existence of specialized receptive units in the brain but might also indicate a fundamental conditioning or learning rather than sensory process. Contrary to our finding of specificity of adaptation to the direction of motion, some investigators have reported effects which do generalize to the opposite direction. In addition, we have found that dissipation of adaptation to motion does not seem to occur over a period of neutral homogeneous stimulation, which result is more characteristic of a memory process than physiological adaptation. And in several experimental situations we have found what appears to be an adaptation in the perceived rate of the passage of time. Since motion is an event over time, it is not certain how much of the adaptation to motion is due specifically to movement. Thus, although the existence of specialized receptive neurons is an undoubted neurophysiological fact, it may not provide an understanding of how perceptual adaptation occurs. Clearly a more refined means of investigating adaptation to stimulus motion is necessary, and we have undertaken to develop a more definitive procedure and apparatus for the purpose.

Another way in which perceptual adaptation is manifested is in the perception of the directions of visual space in relation to gravity. If one is exposed to a tilted visual context, the perceived direction of gravitation will be shifted. With respect to receptive cells in the brain, the question is whether the perception of the orientation of a visual configuration in relation to the orientation of the body depends upon a process locally associated with stimulation by the contours of the lines seen or upon a field-like process set up by the contours. A theory has recently been developed which postulates such a field process for the biological generation of form. In two preliminary experiments we have found the perception of visual orientation to be consistent with this postulated process. It is a mechanism of potentially general theoretical significance in biological evolution and deserves to be pursued further.

The Menstrual Cycle.

Changes in autonomic functioning, time estimation, reaction time, and mood are being observed daily in women over the course of the menstrual cycle and in men given progesterone or placebo in a double blind study. Marked decreases in skin conductance are observed in the luteal phase of the cycle and during progesterone intake. There appears to be a peak in heart rate immediately premenstrually and a preovulatory increase in positive feelings and electrodermal lability.

Problem-Solving.

Those mental processes responsible for resolving the enigmatic situations that challenge the individual in his daily encounters with unfamiliar--and therefore possibly puzzling--aspects of his environment are the objects of an investigation in which people are required to conduct inquiries into the behavioral regularities of well-behaved systems by interacting with them. The results are used in two ways: (1) to assess the methods employed in searching for solutions and (2) to evaluate psychological theories that purport to explain this aspect of human behavior.

In an attribute identification study an adaptation of the selection paradigm was used: the information that was transmitted to the subject was controlled by an algorithm which guaranteed that all isomorphic selections elicited the same amount of objective information. Results indicated that the principal source of difficulty was in the processing or interpretation of information; the repeated failure of the subject to see the implications of data that he had elicited was responsible for prolonging the effort required to reach a solution. However, both the efficiency of inquiry and the ability to interpret data improved with experience. Hence, extensive experience in dealing with enigmas is at least one way to raise the level of heuristic performance.

Another experiment used the reception paradigm, with these findings: information derived from the conservative focus heuristic ("change only one thing at a time") is quite heterogeneous in its value for subjects. In particular, most people fail to use effectively information about which factors are irrelevant in a situation, even when the data are objectively as informative as data concerning those factors that are relevant. This failure is

seen to be especially serious when we recognize that in everyday inquiry a person has no control over which kind of information a query will elicit.

Communication.

This year saw a broadening of studies of conversational behavior in children. The first findings concerned a relatively limited aspect of this process, namely the responses (such as brief vocalizations and head nods) by which listeners signal speakers that they are keeping up with the speaker in the conversation. Last year the initial findings were reported that children give these responses far less frequently than adolescents and adults. This year a prior question was addressed, that of the distribution of adult-type conversation in children of different ages. This question demanded first a definition of conversation in the adult sense, and then a method to apply the definition to children's social behavior. The initial explorations were made at a summer day camp, observing a wide range of children from nursery school to early adolescence as they interacted in their daily camp routines. Among the younger children it became clear (1) that bursts of speech were shorter, and, (2) that the topics were limited almost entirely to comments about the activities they were immediately engaged in. Older children, on the other hand, tended to talk in longer stretches, and their topics concerned more distant events and ideas, or in other words were more abstract. These two differentiating features were consequently used as the bases for a working definition of adult-type conversation.

In order to make quantitative comparisons between different age groups, a systematic observational method was developed for naturalistic settings, and tested in a private school. The data recorded are (1) the number of speaking turns in a five-minute setting, (2) the length of talk for each speaking turn in terms of rythmical units of speech, (3) the number of listener responses, (4) the topic of the conversation, dichotomized as immediate-concrete or remote-abstract, and (5) the distribution of the conversationalists as to number, age, and sex. The numbers obtained in the first three of these factors lend themselves to recording on a special small hand counter, one of which was constructed for this purpose by the Section on Technical Development.

Pretesting this observational protocol on 8th grade children showed that they do occasionally carry on conversational interaction (the frequency of their conversations can only be evaluated when data are collected among older and younger children, in similar situations) and that their rate of listener response is higher than that of younger children observed in a laboratory setting, but lower than that of older adolescents and adults. This method clearly lends itself to collecting quantitative data, and the results can be compared directly with those from experimental sessions in the laboratory.

Concurrent with this work in naturalistic settings, more data from the laboratory were collected during the year, both with children and with adults, thus filling out the results obtained last year. The difference in rate of listener response was upheld with more data, becoming even sharper as more younger children were included. Adults' rate of response is almost three times that of the average of children ranging from 6 to 12 years of age, and

about five times that of children 6 and 7 years. Refinements of experimental instructions to test the effects of situation pull have been introduced, but the number of children so far tested under these conditions is too small for any results to be stated at this time.

Creativity.

This year we completed a study dealing with the measurement of scientific creativity. The major objective of the study was to assess the validities of several popular "creative ability" tests by comparing them to measures of research creativity, and to a number of variables theoretically related to scientific creativity in a sample of adolescents who had evidenced high degrees of motivation and opportunity to exhibit creative behavior in science. Noting that many theorists have conceptualized creativity as a personality trait rather than as an ability trait, a simple test was constructed to illustrate a personality-oriented approach to the measurement of creativity. This instrument was used to provide a baseline against which the validities of the ability tests might be judged. The principal findings were that the personality test predicted creative behavior quite well, but none of the ability tests were associated with the criteria, with the reference variables or with one another. These findings were interpreted as raising questions both about the validity of the ability tests studied and also about the utility of the theories which generated them. The personality test findings were interpreted as demonstrating the potential utility of a personality-oriented approach to the conceptualization and measurement of creativity. However, the test devised was intended for illustrative purposes only and was not to be regarded as a definitive measure of the creative personality.

As a consequence of this study, a creativity scale was developed for the California Psychological Inventory, a general purpose personality inventory. This scale is composed of 29 items, each of which was found to be significantly associated with the measure of research creativity which served as the criterion in the earlier study. This scale was found to possess a high degree of construct validity, being strongly related: (a) to measures of involvement in science, music, art, and other creative fields, (b) to self-ratings of creativity in these fields, and (c) to measures of personality traits theoretically associated with the concept of creativity - independence, ascendency, flexibility, ego strength, cognitive complexity, etc. As expected, the scale is not associated with measures of academic aptitude, academic achievement, or socioeconomic status. These findings indicate that this scale can provide a useful operational definition of creativity in studies testing hypotheses derived from theories about the nature and development of the creative personality.

ANNUAL REPORT OF THE LABORATORY OF SOCIO-ENVIRONMENTAL STUDIES

National Institute of Mental Health

July 1, 1972 through June 30, 1973

Melvin L. Kohn, Chief

For this Laboratory, more than for any other organizational unit of NIMH, this has been the year of the Research Task Force. Six members of the Laboratory have been participating in the intensive review of the Institute's intra- and extra-mural research programs and helping to formulate policy and procedures for the future: Marian Yarrow as co-chairperson of the Study Group on Psychological Processes; Morris Rosenberg and John Campbell as members of the Study Group on Social-Cultural Processes, Rosenberg as chairperson of that group; Carmi Schooler as a member of the Study Group on Mental Illness and Behavior Disorders; Leonard Pearlin and Melvin Kohn as members of the Study Group on Social Problems; with Schooler, Pearlin, and Kohn also serving as members of a special committee on Epidemiology; and Kohn representing the Assembly of Scientists on the Coordinating Committee of the Task Force.

When six of the eight senior scientists in one Laboratory are engaged in an enterprise of this magnitude, the pace of research in the Laboratory necessarily slows down. But we have somehow managed to keep at least some of the research moving forward productively. And we take pride that the scientists of our Laboratory can play so large a role in an effort that promises to have major importance for the future health and vitality of the research programs of the Institute.

The substantive report on our research focuses on new findings and newly formulated projects. As has been our practice in the past, we leave for future reports those studies in which the principal activities of the year were data-collection or the preparation of data for analysis--namely, Leonard Pearlin's study of the social structural origins of stress, for which the data have now been collected and analysis is beginning; Carmi Schooler's analysis of William Caudill's longitudinal data on parent-child interaction in Japan and the United States, for which the data have now been processed for computer analysis; Schooler's continuing experimental studies of the social, psychological, and physiological functioning of schizophrenic patients, on which data are slowly being collected and for which computer programs are being developed; and Gordon Allen's research on behavior genetics, for which population data have now been processed and analysis is beginning.

STUDIES OF YOUNG CHILDREN'S SOCIAL SENSITIVITIES

Continuing their program of research on children's prosocial behaviors, Marian Yarrow, Carolyn Waxler, and Robert King have recently embarked upon a series of studies of the development in young children of altruism and sensitivity to other people's feelings. The earlier experiments (summarized in previous annual reports) have provided answers to a number of questions about the relative effectiveness of different experimentally created child-

rearing conditions for developing altruism (sympathetically based helpfulness) in preschool age children. These findings, in conjunction with the results of other experimental studies of altruism, have raised several further questions: (1) Laboratory studies alone cannot provide information about the origins and unfolding of empathic capabilities. There is a need for longitudinal research, beginning before the child evidences such concerns and charting over time the development of his social sensitivities. (2) Altruism has been studied, to a large extent, in isolation from other intellectual, cognitive, and personality characteristics of the child: How does altruism grow and change in relation to the larger context of the child's changing intellectual capabilities and personality attributes? (3) Finally, what are the practical implications of laboratory manipulations? It is important to attempt to translate procedures optimal for modifying altruism in the laboratory into a set of procedures that can be used to develop or modify the child's concern for others in his own environment. Can these methods be used to produce noticeable, enduring consequences in the child's day-to-day interactions? The investigators are attempting to explore some of these issues in a series of interrelated projects.

One project is designed to document the growth and early development of the very young child's ability to comprehend and respond to other people's feelings and emotional states. There is anecdotal evidence to suggest early sensitivity (e.g., a toddler comforts a crying child by bringing him a toy or putting his arms around him), but this has not yet been buttressed by systematic observations. To provide such information, a longitudinal study is in progress. The study focuses on the second year of life. Thirty youngsters, ten beginning at ages 9-10 months, ten at ages 15-16 months, and ten at ages 21-22 months are the subjects. Each child is to be followed for a period of nine months.

The investigators have chosen to obtain their data in the natural setting of the home environment. Their method of data gathering is unusual: the mothers serve as the primary data collectors. They are carefully trained to observe and to provide detailed accounts of their own youngsters' reactions or lack of reactions when, for example, the child witnesses distress, anger, pain, or happiness in another person. Mothers also record evidences of the child's initiated prosocial and antisocial behaviors, e.g., sharing, snatching, giving affection, hurting. In addition to recording children's responses to naturally occurring feeling states, mothers also portray, from time to time, specified feeling states in the child's presence. This introduces some standardization into the setting, ensuring that similar emotions will be expressed in each home when children are at comparable ages. Periodically, the mother and child are visited by members of the research team to discuss the mother's observations, to observe mother-child interactions, and to obtain additional data about the child, e.g., his imitation, his play, his level of communication. During each visit, one investigator also portrays a specified emotion. This portrayal, in addition to eliciting data, provides an opportunity for simultaneous observation by mother and investigator for an assessment of observer reliability.

A second project is planned in which 3-5 year old nursery school children are the subjects. One part of the study focuses on the child's

growing capacity to recognize that others may have a perspective different from his own. The investigators assume that for a child to behave altruistically he needs to be able to sense that someone else is in a feeling or emotional state that differs from what he is experiencing. Other investigators have found the child at this age to be egocentric, unable to free himself from his own point of reference, cognitively and perceptually, which prevents him from seeing something from another's point of view. The data for this interpretation pertain mainly to the physical world. With regard to the area of feelings and social perspectives, there is little evidence about the child's egocentrism. The intent, then, is to study the child's perspectives in both the physical and the social realms. Children will be observed in a series of experimental situations in both the perceptual and socio-emotional domains in which they are to infer the experience of the other. Further, they will be observed in situations that call for behavioral altruism. Such explorations may help answer the following questions:

1. What are the developmentally changing cognitive abilities of the child to recognize and take the perspective of others with regard to their affective states; and what are the parallels between these abilities and the perceptual-cognitive abilities in the more literal sense involving the physical world?

2. How does the ability to take the "feelings" perspective or role of the other relate to the child's responding altruistically?

The data may provide information about the continuities and discontinuities in development of "role-taking" in the areas of perception, affect, and action.

Further, individual variations in responding will allow the investigators to identify children for whom training would be appropriate. In keeping with their interest in the socialization of unselfish altruism, learning procedures will be instituted, to increase altruistic intervention by the child based on empathic concern for the other. This training will build on the most effective conditions of the investigators' earlier, experimental research. It will incorporate a number of "knowns" about modeling and reinforcement effects and will adapt and elaborate on them to increase the likelihood of the child's developing an internalized and long-lasting desire to help others when the situation calls for it. This training will be conducted in the child's day to day environment, thus remaining real and temperate in the child's ongoing world. If possible, mothers will be enlisted to go through the same procedures with their own children.

DEVELOPMENT OF SELF-CONCEPTION IN CHILDREN

Previous annual reports have told of Morris Rosenberg's comparative analysis of the development of self-esteem in black and white school children, and of children's developing conceptions of social stratification. This year, Rosenberg has completed two new analyses of the development of self-conception in urban school children. As before, the data are based on a survey that he and Roberta Simmons conducted in Baltimore, Maryland, in the spring of 1968.

One analysis focuses on the widely-discussed but little-researched adolescent crisis. Four dimensions of the self-image were considered in this analysis: self-consciousness, stability of the self-image, self-esteem, and the individual's perception of significant others' opinions of him.

The results clearly indicate that the emergence of self-image problems in adolescence is no myth, and that these problems occur early in adolescence. The sharpest rise in disturbance appears between the twelfth and thirteenth birthdays. While the time of onset in self-image disturbance strongly suggests that puberty is of major importance, there is one environmental factor that characteristically intrudes at this life-stage, the transition from elementary to junior high school. Are the 12 and 13-year olds more disturbed because they are older or because they have entered junior high school? One indication is offered by comparing 12-year olds in sixth and seventh grades. Twelve-year olds in junior high school have lower global self-esteem, higher self-consciousness, and greater instability of the self-image than their age-peers in elementary school. These results are maintained when race, social class, and marks in school are held constant.

Further evidence that it is the transition from elementary to junior high school, rather than simply the biological aging process, that is implicated in the adolescent crisis, appears when one examines the self-images of 11 and 12-year olds in the sixth grade and 12 and 13 year olds in the seventh grade. Within the same school class, age makes little difference, but within the same age grouping, school makes a large difference.

Rosenberg's other main analysis this year has concerned the role of "significant others" in shaping the child's self-conception. The theory of reflected appraisals--the idea that the individual comes to see himself as he thinks others see him--has been advanced by such diverse theorists as James, Mead, Cooley, and Sullivan. While the empirical evidence clearly supports this theoretical position, there are substantial discrepancies.

The springboard for this analysis was the hypothesis that it is not only the attitude of the other, but also the attitude toward the other, that affects the self-image. The assumption tested was a simple but neglected one: that not all significant others are equally significant. Two aspects of significance were considered: valuation and credibility. The first deals with whether the individual cares what the other thinks of him, the second with whether he trusts or respects the other person's judgment.

Seven putative significant others were considered: mother, father, teachers, kids in class, boys, girls, and siblings. While the assumption of reflected appraisals was supported in each case, the association between the respondent's perception of the other's attitude and the respondent's own self-esteem was stronger if he valued the other's opinion than if he did not.

This finding led to the obvious question: why are some others especially significant, others less so? While valuation of the favorable opinions of others is bounded by social reality (almost all children care most about

their mothers' opinions of them), there is also an element of volition involved. The data show that the child is strikingly more likely to decide that he cares about the opinions of those who, in his view, think well of him, and to be relatively unconcerned with the opinions of his detractors.

The other aspect of significance is credibility. Much of the locus of self-knowledge in children is external to themselves. For example, children are likely to believe that their mothers know better than they themselves how smart, good, or good-looking they are. Indeed, nearly half think that some other individual knows better than they themselves what they "are like deep down inside." As one would expect, the younger the child, the greater his faith in some external authority's knowing what he really is like.

The importance of source credibility for the self-concept is shown in the data. In each case, the relationship between the perceived self and self-esteem is stronger if the other has high credibility than if he has low credibility. But who has high credibility in the eyes of the child? The data indicate that credibility is in part determined by the motivation to protect and enhance the self-concept. But the individual's location in the social structure, especially his "role-set," is of even greater importance. Both valuation and credibility are affected by the individual's membership groups, statuses, or social categories--his age, race, sex, and socioeconomic status. Social structure and psychological process conjoin to determine who will be more or less significant to the individual and thereby influence his self-image.

SOCIAL ADAPTATIONS AND MOBILITY OF URBAN BLACK POVERTY FAMILIES

During his tenure as a Visiting Scientist in our Laboratory, Professor Albert McQueen of Oberlin College has been analyzing data he previously collected on the ways that poverty level and near-poverty level black families in Washington, D. C., cope with their adverse social circumstances. He has also been collecting a new series of intensive interviews and observations on these processes.

The main objective of this research is to formulate a theoretical model that reveals the essential social processes and structural contingencies embracing the efforts of black families to cope with urban poverty. The two broad types of adaptive problems with which these families must deal are severe resource deprivation and highly devalued social status in situations where there are few institutional supports for maintaining or enhancing family status positions.

Four family types have been identified: the coping poor, the marginal poor, the coping near-poor, and the marginal near-poor. These types denote styles of relative effectiveness in utilizing financial resources for family needs, the coping types being more effective and the marginal ones less effective. The focus of McQueen's efforts is to understand the social and attitudinal bases predisposing parents to employ different coping strategies in the consumption and disposition of resources.

In the earlier research, a survey was made of mothers in 100 poor black families in the Cardoza area of Washington, D. C. At present a series of case studies of 15 to 20 poor black families in the same area is being carried out by McQueen and graduate students at Howard University. They are using intensive interviewing and participant observation methods to gain a more comprehensive picture of the range of coping patterns and consequences.

McQueen's studies show that poor black parents have devised a variety of ingenious consumption and social practices to insure survival and in quest of viable family life under imposed conditions of frequent hunger, recurring crises, and persisting insecurity and uncertainty. In adapting to urban life, uneven employment opportunities, low and often unsteady income, dangerous environments, and other such trying conditions many of these parents develop great strength and perseverance. At the same time, however, such conditions permeate their lives with continuing crises and failures, or at least the omnipresent threat of them. Despite their strong family values and often courageous efforts to realize family aspirations and goals, many poor black parents are pushed into a state of despair and hopelessness and are unable to fend off destructive ghetto forces of compressed misery and exploitation constantly pressing upon their families.

Despite the myriad barriers of racism and limited opportunity, many poor parents do hold onto their social mobility values tenaciously and manage somehow to raise their standard of living, however little, and their sense of worth and respectability. They often must do this at the high cost of sacrificing present consumption and comfort needs in order to convert a portion of their resources into "development capital" for the future. Although many such families are not able to move from the slums, they are geared to creating conditions and opportunities that increase the chances that their children will move up in society. These families McQueen characterizes as incipiently social mobile.

McQueen's approach to the analysis of families in poverty displaces the simplistic notion of "culture of poverty," commonly used to explain the nature and generational persistence of poverty. Not only does his formulation yield a more realistic picture of the richness and diversity of family life under conditions of poverty, but it also holds the promise of providing analytical tools for the systematic study of families cross-culturally and in contrasting socio-economic circumstances. This approach can be instrumental in dispelling value-laden myths and stereotypes about black families that have taken root in social science.

HEALTH ORIENTATIONS OF CHILDREN

The central issue in John Campbell's research is to ascertain how children acquire and modify their perspectives on illness and health. In previous annual reports, we summarized his evidence negating the common-sense view that the child's definition of what constitutes illness is essentially similar to and derived from that of his mother. Is such non-correspondence the pattern for other aspects of health orientations as well?

Comparisons of mothers' and children's normative standards concerning such matters as permissible health-relevant risk taking, standards for open expression of emotion when one is ill, etc., showed a general positive relationship between mothers' and children's views, but the degree of association was not profound. The pattern might best be described as one in which the child's normative judgments parallel but do not equal his mother's. Although correlational analysis showed similarity, it was generally true that children's and mothers' standards were not equally strict. (For example, children's views on health-relevant risk taking are more relaxed than those of the parents.) Correspondence between mother and child is slightly greater for older than for the younger children.

Comparison of mothers' standards, not with children's standards, but with children's reports of their own behavior reveals an interesting pattern that can be illustrated by data concerning health-relevant risk taking. The association between maternal standards and children's reports of their own behavior is highly significant, and this correlation is more pronounced for older children. But although the older child's report of his own behavior is more closely associated with his mother's standards than is the case for the younger child, older children are nevertheless markedly more likely to describe their behavior in a fashion that falls short of their mothers' expected standards. The older child has learned the norms of his parent, has taken them as his own, but in so doing has also taken them with a grain of salt. That is, he apparently makes allowances for his mother's standards, but systematically acts in a measurably "riskier" fashion than his mother would sanction.

RESEARCH ON THE INTERNALIZATION OF RULES, STANDARDS, AND VALUES

Roger Burton has devoted the greater part of the past year to a systematic review of research on moral conduct and to planning new experiments in this area. The main issues covered in this review and assessment of the research literature are the generality or specificity of the behavioral, cognitive-judgmental, and affective components of moral conduct; the situational determinants of honesty; the effects of socialization on such conduct; and a theoretical integration of the findings in a social learning framework. This critical assessment of previous work has served as a basis for planning a new program of experimental studies.

Previous research has shown great situational variability in moral conduct, albeit with some generality across different test situations. This generality has been assessed by analyzing the correlations between the various tests of moral conduct. An alternative approach is to classify individuals according to the consistency of their behavior, to learn which personality and background variables are related to differing degrees of consistency. Analyses again are correlational, providing theoretical leads but only tentative evidence for causal explanations.

Burton has suggested a social learning model for integrating and explaining currently available evidence on the generality or specificity of honesty. This model proposes that the consistency of behavior from

situation to situation is a function of two independent generalization gradients. The first gradient is a physical similarity dimension, essentially the same dimension of stimulus similarity as that ordinarily studied in conditioning and animal learning experiments. The second gradient, cognitive similarity, is essentially the same as that studied in concept acquisition experiments. The model proposes that these generalization gradients combine to determine differences in consistency of behavior. Predictions can be derived from the model about how various child rearing and training techniques would contribute to increasing the consistency in the honesty of an individual's conduct. The studies now being developed will explore these hypotheses about rearing techniques directly, using experimental designs. They will vary factors known to have an effect on the honesty of children's behavior in specific situations, to assess the effects of these variations in other, diverse tests of honesty. The objective is to develop an experimental paradigm that will reliably demonstrate that the various experimental procedures produce differential degrees of consistency in moral conduct. Once this procedure is developed, factors that might affect the additive function of the two generalization gradients will be systematically explored.

OCCUPATIONAL EXPERIENCE AND PSYCHOLOGICAL FUNCTIONING

The principal finding to emerge this year from Melvin Kohn and Carmi Schooler's ongoing study of the social psychology of occupation is that the major finding presented in last year's annual report was right--for the wrong reasons. They concluded then, and can affirm now, that the relationships between occupational conditions and psychological functioning result from a continuing interplay between job and man, in which the effects of job on man are far from trivial.

The research is based on structured interviews conducted in the spring of 1964 with 3101 men, chosen to be representative of all men employed in civilian occupations throughout the United States. Last year's annual report presented systematic evidence that occupational conditions, particularly those that Kohn and Schooler call the structural imperatives of the job, are significantly and substantially correlated with many facets of psychological functioning, ranging from self-esteem to intellectual flexibility. They then examined a number of possible interpretations of these correlations, presenting several strands of evidence, none definitive but all consistent in indicating that the relationships between the conditions men experience in their work and their psychological functioning do not simply reflect some inadequacy in the data; or the effects of education, occupational status, and income; or men's efforts to mold their jobs to fit their needs and values; or selectivity in recruitment and retention. These negative arguments were necessary to establish the plausibility of an interpretive model that assumes reciprocal effects of job on man and man on job. This having been established, the last and crucial step was to assess the magnitude of the reciprocal effects. Here is where they failed last year, and think they have succeeded this year.

Their former approach was to stretch conventional statistical procedures (namely, multiple regression and path analysis), which had been designed to measure the magnitude of effect in situations where one-way

directionality could be assumed, to fit the analysis of two-way directionality. In retrospect, they tried to do the impossible; conventional statistical procedures simply cannot be used to assess reciprocal effects. But they have since learned that econometricians have developed a number of simultaneous equations techniques for dealing with precisely this problem--techniques that are well known and well validated in econometrics but little known and heretofore almost entirely unused in the other social sciences.

In their current analysis, they use the technique called two-stage least squares, a relatively simple method for estimating coefficients in simultaneous equations. The two-stage procedure, in effect, attempts to "purge" each variable of the effects of all others with which it is reciprocally related, by estimating from other pertinent data what each individual's score on that variable would have been if the other variables had not had an opportunity to affect it. These estimated scores are then used for assessing each variable's impact on the others.

As prototypic analysis, they examine the reciprocal effects of the substantive complexity of the job and intellectual flexibility. Substantive complexity is chosen for this analysis because it is the single occupational condition having the most potent psychological ramifications, and also the only one for which they have job-history information fully adequate to the demands of this type of analysis. Intellectual flexibility is chosen because it appears to offer the toughest test: Intellectual flexibility is obviously pertinent to recruitment into substantively complex jobs, and it might be expected to be the most resistant to change of all facets of psychological functioning they have studied.

The analysis shows that the effects of job complexity and intellectual flexibility are, as the interpretive model assumes, reciprocal: each is a major determinant of the other. The model also enables an assessment of the relative magnitudes of effect of substantive complexity on intellectual flexibility and of intellectual flexibility on substantive complexity. The ratio is exactly two to one. In terms of their present reciprocal relationship, the impact of job complexity on intellectual flexibility is greater than the reverse.

It is a simple extension of the interpretive model to consider the relationships between substantive complexity and several other facets of psychological functioning. As before, the crucial comparison is of the effect of the substantive complexity of the job on a particular facet of psychological functioning, as compared to the effect of that facet of psychological functioning on substantive complexity. In all ten comparisons that they are able to make, job affects man more than man affects job. Thus, the substantive complexity of the job is consistently important for psychological functioning, and consistently more so than is psychological function- for substantive complexity.

All this is based on but one dimension of occupation, its substantive complexity. One cannot say whether it is true for the job as a whole, as it is for substantive complexity, that the impact of job on man is consistently greater than the reverse. But one can conclude that in the continuing

interplay between man and job, the effects of job on man are substantial.

But even the application of econometric techniques to the analysis of the reciprocal effects of job on man and man on job cannot definitively show change in particular individuals. Nor does it provide much information about the learning mechanisms involved in transferring the lessons of the job to nonoccupational realms of life. These results cry out for a followup study of a substantial subgroup of the original sample, recording all changes in their occupational conditions since the original survey in 1964, and re-measuring all the principal facets of psychological functioning examined in the earlier study. The followup study is now being planned, hopefully to be conducted within the next year.

Annual Report for 1973

Laboratory of Brain Evolution and Behavior

National Institute of Mental Health

Paul D. MacLean, M.D., Chief

The following report gives a brief statement of purpose and highlights of the work of the three sections of the Laboratory.

In considering the research of the Section on Comparative Neurophysiology and Behavior it should be recalled that the primate forebrain has evolved and expanded along the lines of three basic patterns characterized as reptilian, paleomammalian, and neomammalian. Radically different in structure and chemistry, the three evolutionary formations comprise, so to speak, a triune brain. The Section is utilizing indoor and field facilities for investigating the functions of the two older formations of the forebrain. Authorities have pointed out that after a 150 years of experimentation we are still ignorant of the functions of the striatal complex, which in mammals forms the major counterpart of the reptilian forebrain. The finding that large lesions of the striatal complex may result in no motor incapacity speaks against the clinical view that it subserves purely motor functions. A study has been completed in which lesions were placed in all parts of the pallidal portion of the striatal complex in squirrel monkeys. The results indicate that this structure is essential for the full expression of the species-typical display behavior of this animal. The finding in another study that lesions of the corpus striatum interfere with the nest building behavior of mice provides additional evidence that the striatal complex plays a basic role in genetically constituted, species-typical behaviors.

Two studies have provided additional evidence that dopaminergic systems ascending from the midbrain to the olfactory striatum and corpus striatum exert an "energizing" influence on an animal's behavior. Comparative observations on the parrot, turkey, opossum, and monkey reveal that apomorphine (believed to act on dopamine receptors of the striatum) induces aimless, increased activity of the animal. On the contrary, it has been found in the squirrel monkey that damage by 6-hydroxydopamine to the dopaminergic systems at their origin in the midbrain results in a state of incapacitation resembling parkinsonism.

The limbic system corresponds to the paleomammalian formation. Two other ascending aminergic systems containing norepinephrine and serotonin, respectively, are particularly identified with limbic structures. In cooperation with the Laboratory of Clinical Science it has been found in a comparative histofluorescence study (including the pygmy marmoset and squirrel monkey) that the organizational pattern of these phylogenetically ancient aminergic systems, as well as the dopaminergic system, has been preserved with remarkable consistency in the evolution of primates.

The septum, which is a central subcortical structure of the limbic system, contains numerous norepinephrine terminals and is closely allied to the olfactory striatum. It has been shown in a group of mice living under simulated natural conditions that septal lesions result in a transient alteration of aggressive behavior and an enduring deficit in nesting behavior.

Work has continued on olfactory and interoceptive inputs to the limbic system. For the first time evidence has been obtained suggesting that olfactory projections via the anterior commissure may afford sparing of olfactory function following bilateral section of the lateral olfactory tract. Contrary to classical views, and relevant to phylogenetic aspects of learning, testing with an improved olfactometer has revealed that rats acquire learning sets at levels comparable to those achieved by primates in other kinds of discriminations.

With the use of an improved technique for vagal stimulation in chronically prepared monkeys, it has been shown that vagal volleys evoke unit responses in the medial dorsal nucleus. It is worth pointing out in connection with the withdrawal symptoms of addicted individuals that little is known about the cerebral representation of visceral functions.

The Section on Comparative Biopsychology conducts comparative and ontogenetic studies on the effects of neonatal experiences on temperament, motivation, and learning ability. Because of the natural ties between human beings and dogs, there are special advantages in using dogs for such studies.

It has been found that the performance of the neonatal dog in escape and avoidance behavior is superior to that of the neonatal mouse or kitten. It is widely held that young animals are deficient in behavior requiring inhibition. Passive-avoidance studies on neonatal beagles, however, and other

experiments conducted by this Section, have demonstrated that there is a capacity for inhibition in animals under two weeks of age. In another study it has been shown that the presence of a passive human being is as powerful a reinforcement as food. There is the notable difference, however, that beagles fail to show extinction in tests run without the passive person.

Next year a collaborative study is planned with the Section on Comparative Neurophysiology and Behavior to observe the effects of early injury to the corpus striatum on later development and breed-specific behavior.

The research of the Section on Behavioral Systems has been largely devoted to an investigation of the effects of crowding on social interactions and reproductive behavior of animals. Last year was a landmark year for this Section, having seen the termination of a five-year experiment on a population explosion of mice. Population growth terminated when the density reached twenty times the number of mice that would be expected to inhabit the same amount of space under ordinary conditions. In keeping with predictions, over the past two years there were no surviving young, and approximately the last thousand mice born exhibited no capacity for territorial, courtship, and reproductive behavior. The last mouse died on January 8, 1973.

Three findings have emerged from this long-term study that possibly have human implications: (1) The conditions of crowding initially lead to increased fertility. There seems to be a human parallel here, insofar as a recent, independent demographic study conducted in Chicago revealed the surprising finding that regardless of economic status, education, or ethnicity, fertility increased with crowding. (2) Excessive crowding in the mouse colony resulted in so many interactions among individuals, that in addition to the disruption of parental care, it was impossible for the progeny to acquire and perform the sequences involved in territorial, courtship, and reproductive behavior. As judged by measurements of "velocity" (a term applying to interactions) most animals became socially withdrawn, engaging in fewer actions than the low member of a control group of optimum size. Of great theoretical interest, there developed another type of animal characterized by a splendid pelage (the so-called "beautiful ones") that were as deficient as the withdrawn animals in territorial, courtship, and reproductive behavior. (3) Finally, it was found that in re-establishing selected behavioral types of the overpopulated community in groups of optimum size there was little or no recovery of territorial, courtship, or reproductive ability.

In other words, a point is reached in overpopulation where rehabilitation becomes impossible. This would appear to be the first time that it has been demonstrated experimentally that the untoward behavioral effects of excessive crowding are irreversible.

Annual Report of the Laboratory of Cerebral Metabolism
National Institute of Mental Health
Louis Sokoloff, Chief
July 1, 1972 through June 30, 1973

The Laboratory of Cerebral Metabolism has continued during the last year to pursue research projects initiated in previous years but which have in some cases been diverted into somewhat new directions with potentially exciting results. The Laboratory remains organized in three Sections which pursue independent and distinct lines of research within the range of interest and competence of their Section Chiefs. The confederation of these Sections into a single laboratory organization confers, however, a number of advantages to the members of the Sections and their research programs. These are derived from the association of a critical mass of skilled and motivated investigators who help each other by exchange of criticism, advice, and ideas. In addition, there are the usual benefits to be derived by the coordinated sharing of major equipment, resources, facilities, and emergency situations regarding personnel.

Section on Developmental Neurochemistry
Louis Sokoloff, Chief

This Section continues to pursue a broad program of investigations of normal and pathological mechanisms underlying normal and abnormal growth, development, and maturation of the nervous system. It is also engaged in elucidation of the relationships between metabolic changes in the central nervous system and alterations in functional activity in health and disease. These studies are carried out at both the biochemical and physiological levels. No new projects were initiated this last year. Some of long-standing duration continue to make steady progress. Others initiated more recently have now progressed through the lead time of methodological development and trial and in some cases have assumed a momentum with substantial and potentially exciting results.

The thyroid hormones are known to play an essential role in the development and maturation of the nervous system. Thyroid deficiency in early postnatal life leads to physical dwarfism and mental retardation, a condition known as cretinism. The elucidation of the mechanism of action of thyroxine, the major thyroid hormone, has been a long and continued interest of the Section, and its studies led several years ago to the discovery that

thyroid hormones stimulate protein synthesis. This action is now recognized as the basis of many of the numerous and diverse physiological effects of the hormones. The Section has been engaged in studies of the molecular mechanisms of the thyroxine stimulation of protein synthesis in brain and other tissues. It has been found that the stimulation of protein synthesis is not a direct effect of the hormone on the process of protein synthesis but is mediated by the product of a prior energy-dependent reaction between the hormone and the mitochondrial fraction of the cell. These studies led to the explanation of the loss of thyroxine-sensitivity which occurs in brain as the brain matures and the failure of thyroxine treatment to reverse the mental retardation of cretinism after a critical age is achieved. Mitochondria of immature brain are capable of reacting with the hormone in the initial essential reaction, but the mitochondria of mature brain have lost this capability. The identity of the active product of the thyroxine-mitochondrial reaction and the chemical nature of this reaction are obviously key questions to be resolved, and the pursuit of these questions are major goals of the Section. Substantial progress has been made in determining the properties of the active factor, and these properties have been utilized to design purification procedures. Its exact identity is still unknown, but studies are continuing and progress being made.

Studies have been continuing on defining the differences between mature and immature brain mitochondria. One of the differences which was previously found in this Laboratory was in regard to their content of D-β-hydroxybutyrate dehydrogenase, an enzyme which is important in the utilization of ketone bodies. This enzyme, which is confined only to the mitochondrial fraction of the cell, is low in the brain at birth, rises to a peak during maturation, and then, in contrast to other mitochondrial oxidative enzymes which remain constant, declines again in the mature brain. It has recently been found that these changes in enzyme activity are temporally correlated with changes in blood composition caused by dietary factors. The rise in enzyme activity in brain closely follows the development of ketonemia caused by feeding on fat-rich maternal breast milk. The decline in enzyme activity begins immediately after the animals are weaned onto a normal high carbohydrate diet and are recovering from the ketonemia. Starvation produces ketosis at any time of life and is also associated with increased utilization of ketone bodies mediated by this enzyme. It is clear that this enzyme, which allows the brain to switch to utilization of ketone bodies derived from fat

degradation when its glucose supply is endangered by starvation or by high fat, low carbohydrate diets, is in some way regulated by or in concert with the availability of dietary factors. Recent studies by Dr. Grave in this Laboratory have shown that the entire developmental pattern of this enzyme in brain is shifted on the time scale to a younger age in infantile hyperthyroidism, indicating that it is also under hormonal control. When added directly to the enzyme *in vitro* thyroid hormones inhibit the enzyme activity by lowering its affinity for its substrates. Evidence has been accumulating for a number of years that thyroid hormones frequently inhibit DPN^+-linked dehydrogenases. Its action on D-β-hydroxybutyrate dehydrogenase may serve as a model in which to study its mechanism of action. Studies have, therefore, been in progress to solubilize and purify this membrane-bound mitochondrial enzyme. During the last year the enzyme has been successfully solubilized by Dr. Fitzgerald and Dr. Kaufman, and progress toward its purification is now proceeding fairly rapidly. One benefit already derived from these studies is the finding that the enzyme's activity is completely dependent on the presence of a mitochondrial lecithin, and progress toward the purification and identification of the species of lecithin is also being made. The enzyme is also being purified from liver for comparative purposes. It is hoped that the availability of the purified enzyme will allow more definitive studies of the mechanisms of regulation of the enzyme's activity in brain by dietary factors and thyroid hormones.

The interaction of thyroxine with mitochondria has long been known to stimulate latent mitochondrial ATPase activity. In contrast, studies in this Laboratory have demonstrated that the hormone inhibits microsomal ATPase activity. Microsomes have a number of ATPases which are stimulated by various ions and are believed to be involved in the transport of the ions in and out of the cells. Ion transport is fundamentally involved in the maintenance of membrane potential and excitability as well as many other cellular functions. Thyroxine inhibits all the ion-stimulated ATPases. The effect was originally found with liver microsomes, but studies in the last year have shown that the effect is even more prominent in brain preparations and in isolated liver plasma membranes. It was recently found that when administered *in vivo*, thyroid hormones caused an increase in the amount of microsomal ATPases in liver but not in brain. Whether this represents a specific action of the hormone or a cellular regulation to compensate for the inhibition of the existing enzyme activity by direct action of the hormone is under study. Methods are also being developed to investigate

the effects of thyroid hormones on intracellular ion concentrations in the intact animal.

Protein synthesis in brain is relatively high early in life and declines progressively during development until it reaches a relatively low level at birth. Much of this decline is attributable to a change in the protein synthetic activity of the ribosome. It is interesting that the decline in protein synthetic activity bears an almost inverse relationship to the development of the hormone-sensitive cyclic AMP system in the brain. Since cyclic AMP is now known to act by stimulating protein kinase, an enzyme which phosphorylates proteins, the possibility has been considered that the changes in ribosomal activity with maturation of the brain reflect the effects of phosphorylation of brain ribosomal proteins. Studies by Dr. Schmidt during the past year have demonstrated that cAMP-dependent protein kinase is present in brain microsomes, and brain ribosomes are capable of being phosphorylated by this enzyme all through life. The possibility remains that differences in the degree of phosphorylation of the ribosomal proteins in vivo may regulate the activity of the ribosomes in protein synthesis. Studies in progress are designed to determine whether, in fact, ribosomal protein phosphorylation does influence the rate of protein synthesis.

Drs. Kennedy, Des Rosiers, and Mrs. Jehle, in collaboration with Dr. Patlak of the Biometrics Branch, have made spectacular progress this year in the development of a method which for the first time will permit the quantitative measurement of glucose metabolism in the individual component functional and structural units of the brain in conscious animals. The method is already at a usable level, but several experiments remain to be done which should refine further its precision and accuracy. After a series of validation experiments, it will be used to study the effects of sleep, anesthesia, functional activity, epinephrine-induced anxiety, etc. on the glucose metabolism of individual nuclei or groups of cells in the intact animal. The method has already been used to confirm what has long been hypothesized but not hitherto verified that the blood flow in the individual parts of the brain are adjusted to their local metabolic rates.

Section on Myelin Chemistry
Marian W. Kies, Chief

This Section has continued its investigations of the relationship between the structure of myelin basic protein and

its activity as an immunologic agent in inducing the disease, allergic encephalomyelitis (EAE). A major immediate goal of the Section has been to explain the immunologic reactivity of the basic protein in terms of its primary structure, i.e., to identify the specific amino acid sequences which are capable of either combining with antibody or inducing cellular sensitivity. Induction of delayed hypersensitivity is currently thought to be related to induction of EAE. The sites responsible for induction of EAE are species-specific; for example, in different species EAE is induced by different regions of the basic protein molecule although some sites on the protein are encephalitogenic in more than one species. Several regions of the molecule responsible for induction of EAE in a variety of animals have been identified by a number of investigations including those of this Section, for example, Dr. Martenson and Mrs. Deibler, who found the occurrence of two rat myelin basic proteins, both encephalitogenic and identical except for the deletion of a defined sequence of amino acids in the smaller one.

According to basic principles of immunology, the induction of antibody by a protein antigen results from recognition by certain cells of the lymphocytic line of specific regions of the antigenic molecule. Recognition is followed by proliferation of specific cell lines which subsequently produce antibody structurally related to the amino acid sequence responsible for triggering the proliferative response. Thus, a method capable of demonstrating binding of antibody to a specific region of the molecule defines the sequence responsible for the original "recognition" phenomenon. During the past year the Section has made major efforts toward the characterization of these antibody-combining sites in myelin basic protein. These studies have required the establishment and application of a variety of techniques, such as the fragmentation of the protein molecule by enzymatic and chemical treatments, the isolation, purification, and characterization of the isolated fragments, the induction of antisera containing large amounts of antibody to basic protein by different types of immunization, and the preparation of radioactive derivatives of the fragments and the analyses of the ability of the different antisera to bind the labeled fragments of the myelin basic protein. Through the combined efforts of Drs. Martenson and Driscoll and Mrs. Deibler and Mr. Kramer, several modified myelin basic protein species and polypeptide sequences derived from different portions of the protein have been isolated and characterized. Dr. Driscoll has utilized fragments of guinea pig myelin basic protein to analyze various

antisera prepared from guinea pigs immunized with whole guinea pig protein and/or the modified basic protein by Mr. Stream. Mr. Blum is engaged in similar studies in the rabbit. The results of the guinea pig study indicate three distinct regions of the basic protein molecule which are capable of binding antibody. The specific amino acid sequences in each of these regions remain to be defined.

Even though the etiology of multiple sclerosis remains obscure, the pathogenetic mechanisms involved are generally believed to be related to an abnormal autoimmune reaction in the CNS of the patient to myelin basic protein. Thus, studies of the type in progress in this Section which are directed at the characterization of the immunologic reactivity of this protein can be expected to provide a rational basis for the design of safe and effective therapies for multiple sclerosis.

Section on Membrane Chemistry
Louis Sokoloff, Acting Chief

A number of laboratories, including this Section, have observed that acetylcholine stimulates the incorporation of phosphate into phosphatidic acid and phosphatidylinositol in preparations from neural tissues. Phosphatidylinositol is an important phospholipid component of membranes, and it is widely believed that this biochemical effect is related to the mechanism of action of the neurotransmitter at the specific receptor site on the membrane of the effector cell. The mechanism of the action of acetylcholine on phosphoinositide metabolism is still unknown, but previous workers in this Section proposed that acetylcholine stimulates the rate of hydrolysis of phosphatidylinositol leading to increased levels of diglycerides which are now available for phosphorylation to phosphatidic acid and then esterification back to phosphatidylinositol. In this way acetylcholine could stimulate phosphatidylinositol turnover. Recent studies in this Laboratory have implicated calcium ions in phosphatidylinositol turnover. EGTA, a potent chelator of Ca^{2+}, has been found to markedly inhibit $^{32}P_i$ incorporation into phosphatidylinositol, and this inhibition can be reversed specifically by the addition of excess Ca^{2+}. Evidence has also been obtained that Ca^{2+} stimulates the hydrolysis of phosphatidylinositol. In other words, Ca^{2+} appears to have actions similar to the mechanisms postulated for acetylcholine. This suggests the inositol turnover is mediated via an effect on free Ca^{2+} levels. The studies demonstrating a role of Ca^{2+} on phosphatidylinositol

turnover have been completed and published during the last year. Those directed at relating Ca^{2+} to the mechanism of the acetylcholine effect are still in progress.

Evidence has been accumulating that all transmitters cause the same effects on phosphatidylinositol turnover as acetylcholine, but specifically only in their target cells. The specificity to the transmitter is conferred by the receptors in the target cell, but the response is the same and may, therefore, represent the effects of excitation. Since evidence is also available to indicate that cAMP mediates the effects of adrenergic neurotransmitters and cGMP mediates those of acetylcholine, the possibility must be considered that cyclic AMP and cyclic GMP are responsible for the effects of the transmitters on the turnover of phosphatidylinositol. Studies designed to test this hypothesis have been initiated recently, and the results are quite promising that the hypothesis is valid.

Annual Report of the

Laboratory of General and Comparative Biochemistry

National Institute of Mental Health

Giulio L. Cantoni, Chief

1973 has been a year both of transition and achievement. A number of projects have reached fruition and others have been initiated. The overriding problem has been, and continues to be, the limitation to growth imposed by the budgetary considerations. These limitations have not affected our work insofar as procurement of equipment or supplies, but are affecting our overall capabilities because of manpower shortages in all phases of our work. We can only hope that no further decrease in our personnel will be necessary and that we can learn to cope with present limitations.

Studies in Dr. Cantoni's group on protein-nucleic acid interaction, transmethylation and transalkylation reactions and RNAase H have continued, albeit at a slower pace because of personnel shortages due to the freeze on new appointments. A number of projects have been brought to fruition as shown by their description in published form, but the rate at which they will continue to develop will depend on improvements in the personnel problem. At the present time, however, Dr. Cantoni's group is inadequately staffed.

Dr. Cantoni and his collaborators have succeeded in elucidating the subunit structure of a homogeneous preparation of seryl tRNA synthetase and supplied kinetic and other data bearing upon the mechanism of interaction between small molecular weight substrates, the enzyme protein, and the acceptor RNA. Detailed understanding of these sorts of interactions are expected to shed light upon a problem central to many of the major problems in biology, i.e., the general area of nucleic acid-protein recognition and interaction. With Dr. Haberkern, he has developed a method of purifying the enzyme in calf thymus extracts which hydrolyzes specifically the RNA portion of RNA-DNA hybrids. The purified enzyme has been used to characterize the substrate acted upon and the products formed by this unique enzyme. The biological role of this widely distributed enzyme represents a major puzzle, the answer to which will surely be useful in understanding normal and abnormal processes of information transfer in biological systems Dr. Schmidt and Dr. Cantoni have taken the first steps toward a study of spermidine metabolism in mammalian brain. There is increasing evidence that this compound, or related ones, may play a role in the regulation of growth processes and the early indications coming from their work that there may be a correlation between the rate of spermidine formation and the times of most

rapid brain tissue formation and myelinization raise important questions which will surely stimulate a great deal of work.

Two important new projects were initiated: the studies of S-adenosylmethionine analogues and in vitro muscle differentiation. The first is really an outgrowth of work on trasmethylation that has been pursued in the laboratory since its inception and which has become feasible through the awarding of a contract to Dr. R. Borchardt of the University of Kansas. The other is one of the results of Dr. Cantoni's foreign work assignment. His achievements during the foreign work assignment are reviewed in detail in Project 63.

Dr. Klee, together with Dr. K. S. Iyer and C. Klee, have been continuing their studies of the interaction of the two proteins which comprise the lactose synthetase system. A fully guanidinated derivative of α-lactalbumin has been prepared which is functionally identical with the unmodified protein and which by virtue of a radioactive label incorporated via guanidination will allow a study of the interaction of this material with membrane bound galactosyl-transferase. With the aid of newly devised methodology, the four disulfide bridges of α-lactalbumin were found to be extraordinarily easily reduced to sulfhydryl groups at room temperature and to be composed of two classes. One class, comprising three disulfides is resistant to reduction at temperatures near 0^{o}. The second class, composed of a single disulfide, is easily reduced even at low temperatures. This disulfide bridge has been identified as linking cysteinyl residues 6 and 119, which are very close to the two termini of the polypeptide chain. These studies imply that the structures of lysozyme and of α-lactalbumin are not as similar as had been previously believed. The nature of the forces involved in the interaction of α-lactalbumin and galactosyl-transferase is also being studied. Binding affinity increases with decreasing temperature and is decreased markedly by raising the ionic strength. Thus ionic, but not hydrophobic forces play a major role in the stability of the complex.

In the past few months, Dr. Klee has initiated a new project which has as its ultimate goal an understanding of the mechanism of action of narcotic drugs on the biochemical level. Very preliminary findings only have been made to date which indicate that it will be possible to study the binding of narcotics such as morphine and methadone to specific sites in brain particulate preparations and also their effects on the flux of some neurotransmitters through membranes.

In Dr. Merril's group, the observation that bacterial genes can function in a human galactosemic cell line has been extended to three new human galactosemic cell lines. These experiments have yielded strong genetic evidence that the bacterial gene is

undergoing transcription and translation. A major effort is being made to corroborate this finding by the use of differential enzyme inhibitors. Such a demonstration would further prove that the enzyme which appears in the galactosemic cells is in fact a bacterial enzyme. Preliminary studies have been completed on the fate of bacteriophage in a mammal, the mouse, so that experiments to detect the function of a bacterial gene in a whole organism can be attempted. The initial observation of Merril and his collaborators that bacterial genes function in eukaryotes has been confirmed by Carlson and Doy et al. (PNAS 70: 598 and 723, respectively). The discovery of bacteriophage in commercial serum used for tissue culture preparations and vaccine production has also been confirmed by the FDA and our prediction of phage contamination in human vaccines has been borne out.

During the past year research activities in the Section on Alkaloid Biosynthesis have continued along previously indicated lines. Drs. Giovanelli and Datko have extended their investigations into the nature of the physiological α-aminobutyryl donor in cystathionine biosynthesis to new plant materials grown free of foreign microorganisms. In view of the extremely low concentration of the physiological substrate, now firmly established as O-phosphorylhomoserine, this is a very important extension of the investigation which eliminates the possibility that previous positive findings were due to contamination. Various methodological improvements have been made, also, which give us the capability to attack fundamental problems concerning methionine biosynthesis in plants in a sufficiently comprehensive manner so that we may expect to relate our in vitro enzyme studies to the underlying physiological situation. The chief requirements now are time and manpower to attack the many problems which these methods render experimentally approachable.

Studies of inborn errors of human sulfur amino acid metabolism have also been pursued. Balance studies of cystathionine synthase deficient patients have supplied a tentative estimate of the human requirement for cysteine, a fundamental value not heretofore available. The concept of a sulfur balance has been developed and a beginning has been made into experimental determination of this balance in various conditions of diet and disease. A firm demonstration has been provided of the possibility of treating human genetic disease by means of partial restitution of the deficient enzyme activity. As these steps have been taken, attention must also be directed to the losses in several areas which make it highly likely in Dr. Mudd's and my view that our rate of progress will be sharply curtailed in the near future. These losses are: (a) The complete lack of any future possibility to carry out clinical studies which is threatened by apparently imminent changes in the Digestive and Disease Branch, NIAMDD. (b) Ambiguity, stresses and changes in

Dr. Uhlendorf's situation have severely and adversely affected his collaboration with the Section on Alkaloid Biosynthesis and the Section's tissue culture capabilities. It is hoped that this is a temporary situation and that it will be possible to recoup from these developments by the arrangements that are being worked out at the present, but that remains to be seen. (c) The diversion of considerable amounts of Dr. Mudd's time and energy to duties connected with the Task Force during the previous year. Since the studies of human genetic diseases have been essentially a one man operation as far as support from this Section, this diversion has forced a delay in many ongoing aspects. For example, it has not been possible to follow-up the lead developed last year with the discovery of a biochemical disease which is accompanied in one patient by treatable schizophrenia. Hopefully, this diversion is drawing to a close, but the combined effects of these various losses on immediate momentum and long-range capabilities are likely to be very severe. It has already been necessary to forclose several avenues of research requested by collaborators in Universities because Dr. Mudd did not think he could honestly undertake any new projects at a time when his research capabilities were rapidly dwindling. It must be realized that this failure to initiate new projects will become most evident several years from now at a time when these projects might have been expected to come to fruition. Given the present situation, this process is likely to continue, or to be aggravated. It is realized that these curtailments are part of a general process of winding down of support for biomedical research. Nevertheless, we feel it is necessary to point out the implications of these changes for the areas with which we are most familiar and responsible.

The desirability to consolidate several lines of work utilizing tissue culture techniques (Dr. Mudd's work on homocystinuria and other diseases of sulfur amino acid metabolism, Dr. Merril's work on galactosemia and Dr. Cantoni's work on muscle differentiation *in vitro*), has suggested the establishment within the Laboratory of a unit on tissue cultures. This development was also stimulated by the unforeseen development in the Division of Biologics Standards that had adversely affected the potential for continued collaboration with Dr. Uhlendorf, who for several years had been associated professionally with Dr. Mudd and his collaborators on work involving tissue cultures. As a result of these developments, Dr. Uhlendorf was brought into the laboratory and a new unit is being organized to house tissue culture work. The transition has not yet been completed and the final outcome of this arrangement is still to be determined. There is no doubt, however, that it will be useful to have within the laboratory the capability and expertise on tissue cultures rather than depend on collaboration with outside groups.

ANNUAL REPORT OF THE LABORATORY OF NEUROBIOLOGY

NATIONAL INSTITUTE OF MENTAL HEALTH

Ichiji Tasaki, Chief

In the past year the Laboratory of Neurobiology has carried out investigations on the nervous system at several levels: the macromolecular events associated with nerve excitation, the physicochemical characterization of membrane component interactions, and the mechanism of visual-motor integration in the monkey brain.

Experiments on nerve excitation have succeeded in further elucidating the macromolecular events associated with an action potential. Squid giant axons and crab or lobster nerves were stained with fluorescent dyes, and a spectral analysis was made of the change in fluorescence occurring during an action potential. The light contributing to the change in fluorescence intensity was found to have a narrower and sharper spectrum than the spectrum of the fluorescent light arising from the labelled axons at rest. Birefringence changes were also observed and used to explain changes in the macromolecular membrane structure. Variation in temperature was found to cause an abrupt transition in membrane potential which was interpreted as indicating a phase transition in the axon membrane during excitation. Labelling the internal and external membrane protein was performed with I^{125} before and after potassium depolarization. The depolarized state appeared to decrease the efficacy of iodination of the proteins of the internal membrane surface layers. These data provided further evidence supporting the hypothesis that a hydrophobic-hydrophilic transition as well as a phase transition occurs in the membrane during nerve excitation.

Several aspects of the structure and interactions of membrane components were investigated using fluorescent probes and circular dichroism spectra. The water content and mobility in red cell membranes were monitored with the hydrophobic probe dyes 1,8-ANS and 2,6-TNS. The location of membrane-calcium binding sites were determined using the calcium sensitive fluorescence spectra of the tetracycline dyes. Protein conformation was analyzed via circular dichroism spectra for both the membranes and storage proteins of chromaffin granules.

Experiments on the visual system concentrated on the visual and motor functions of the frontal eye fields of the frontal cortex, on the "attention" effect reported previously, and on the role of the superior colliculus in head and eye movement. Cell responses were studied in relation to visual stimulation and eye movement in awake monkeys trained in a behavioral task. First, contrary to the general view that the frontal eye fields are involved in generating eye movements, no cells were found to discharge prior to eye movement in the area. Instead about half of the cells responded to visual stimuli; the type of response was similar to that seen in superior colliculus rather than striate cortex. The frontal eye field areas are therefore not motor areas

for eye movement but rather are more likely to be involved in some integration of visual information related to eye movement. Second, in frontal eye fields we have seen an enhancement of cell discharge when the monkey attends to the stimulus that is activating the cell similar to that which we have reported previously for the superior colliculus. No such enhancement was seen in the visual cortex indicating that the selective facilitation of some visual inputs takes place at levels beyond the primary cortical visual area. Finally, in the superior colliculus cells have been found to discharge before eye movement not before head movement. The superior colliculus therefore does not integrate visual information for both head and eye movement but rather for eye movements alone.

Annual Report of the Laboratory of Neurochemistry

National Institute of Mental Health

Seymour Kaufman, Chief

During the last year there were several important advances made in the Laboratory.

One of the most significant of these was the detection, for the first time, of phenylalanine hydroxylase activity in a biopsy liver sample from a patient with classical phenylketonuria (PKU). The activity is only 0.27% of the normal level.

Prior to this finding, the nature of the defect in this disease, at the molecular level, was a total mystery. The detection of hydroxylase in this patient answers several important questions about the disease.

1. PKU is not caused by a deletion mutation since a gene product has now been detected. The disease is therefore probably caused by a mutation that leads to an amino acid substitution. The mutant enzyme has low hydroxylase activity and is kinetically-distinguishable from the normal enzyme.

2. Since the mutant enzyme can now be detected by its activity, it can for the first time, be characterized in terms of its kinetic and regulatory properties. These properties may ultimately reveal novel ways in which this low activity can be enhanced.

3. The low hydroxylase activity can now be used as an assay for the eventual isolation of the mutant enzyme. Its isolation would allow for its physical and chemical characterization. To accomplish this goal, however, one would need a moderate amount of fresh liver from a PKU patient.

4. The finding that there is some, albeit a very small amount, of the hydroxylase makes it logical, for the first time to attempt to enhance this activity in vivo. If such attempts were successful, an alternate form of therapy for PKU might be developed. This is one of the compelling reasons for studying the regulatory properties of the normal enzyme (see below).

At first glance it might appear that chances for achieving a therapeutically-significant enhancement of the hydroxylase activity would be hopelessly remote. After all, a 400-fold increase would be required to raise the level of activity to normal. We know, however, that the normal activity represents a comfortable excess. We know this from our previous work which showed

that patients with hyperphenylalaninemia who have no signs of mental retardation have only about 4% of the normal hepatic levels of phenylalanine hydroxylase. These results suggest that the enhancement factor in the hydroxylase activity that must be achieved in PKU is not 400, but rather 14. And, it should be added, the figure of 14 is a maximum value; it seems likely that significant ameleoration of the symptoms of PKU could be achieved by increasing the hydroxylase levels by only three or four-fold.

The work on PKU provides a vivid illustration of the dynamic interaction between fundamental studies on an enzyme system and clinical studies in a closely related area. Thus, the detection of hydroxylase activity in PKU liver was based on the development of a highly sensitive assay for hydroxylase activity. This assay, in turn, was based on the delineation of about a dozen separate properties of the hydroxylating system, the most recent of which was the marked activation of the hydroxylase itself by phospholipids. If the discovery that PKU patients possess some hydroxylase activity is a key that may unlock new doors in the future, this key was fashioned from studies of the properties of the normal enzyme system.

As indicated above, one of the routes to a possible enhancement of the hydroxylase activity is through a study of the regulatory properties of the normal enzyme. Last year we found a new way in which the activity of the purified enzyme from rat liver can be enhanced. By limited digestion of the hydroxylase with a protease, an enzyme molecule only two-thirds the size of the native enzyme is formed. This partially digested hydroxylase is about 30 times more active than the undigested enzyme. Furthermore, the kinetic properties of the smaller enzyme are indistinguishable from those of the native enzyme after activation by certain phospholipids.

It is possible that partial proteolytic digestion is a physiologically-important mechanism for the regulation of the activity of the hydroxylase. This process would depend on the stability of lysosomes in the liver cell. Agents that can labilize the lysosomal membrane and thereby release intracellular proteases, might be capable of activating the hydroxylase *in vivo*.

An important advance was made in the problem of the regulation of catecholamine biosynthesis. Using pure tyrosine hydroxylase (isolated from bovine adrenals by an extension of our procedure) as the antigen, we have prepared a specific antiserum to the enzyme. The antiserum does not react with any of the following enzymes: hepatic phenylalanine hydroxylase, brain tryptophan hydroxylase, adrenal dopamine β-hydroxylase or mouse melanoma tyrosinase. On the other hand, there is extensive cross-reactivity between the antiserum and tyrosine hydroxylase from bovine, rat, monkey and rabbit adrenal glands as well as from bovine caudate and human pheochromocytoma.

Annual Report of the Laboratory of Neurophysiology

National Institute of Mental Health

Edward V. Evarts, M.D., Chief

July 1, 1972 -- June 30, 1973

This summary of the research program of the Laboratory of Neurophysiology will describe four areas of ongoing research according to which the ten projects of the Laboratory may be categorized: 1) Cellular Physiology, 2) Central Control of Movement, 3) Neural Correlates of Learning and Memory and 4) Neurochemical and Neuroanatomical Correlates of Behavior.

I. Cellular Physiology. This general area includes four projects, two under the direction of David Carpenter and two under the direction of Stanley Rapoport. One of Carpenter's projects has investigated the ionic and metabolic basis of neuronal thermosensitivity. An understanding of these mechanisms is important not only in the development of an understanding of how the brain works, but also in pursuit of rational approaches to treatment of neuronal diseases by drugs. Carpenter's experiments attempt to study these elementary processes in simple nervous systems and then to test the conclusions in mammalian nervous systems. In the case of neuronal thermosensitivity he has isolated several temperature-dependent processes which will be tested in mammalian preparations. His study of the ionic basis of neuronal pacemaker discharge in the mollusk also has relevance to the mammal. The neuronal pacemaker functions in a manner very similar to that of the heart.

A second project under the direction of Carpenter is aimed at investigating the state of ions and water in living cells. His results to date suggest that ions in nerve cell bodies exist in a very different state from those in axons. If this be true it is necessary to reexamine many of the concepts which were developed to explain electrical events in axons and which have been assumed to apply to all excitable tissues on the assumption that all ions are free. Moreover, it seems very possible that the state of ions in most cell bodies may be more like that in Aplysia neurons than that in squid axons since the cell bodies contain many more membraneous structures and a higher concentration of organic molecules (which are probably the site of the ion and water binding). These observations, therefore, may have relevance to all types of cells.

Studies in the general area of cellular physiology have also been carried out by Stanley Rapoport. One of his projects has focused on the electrical, ionic and physical properties of muscle. This research is important to our program because a knowledge of mechanical properties of the

components of muscle and of their relative contribution to tension as a function of stretch is required to understand the process of contraction. Correlation between electron microscopic structure of the sarcolemma and myofibrils and their properties permits a better understanding of the molecular forces regulating muscle contraction.

It is known that stretch prolongs frog muscle survival and stimulates muscle metabolism. These effects have not been interrelated up to now, but Rapoport's work now shows that they may be related through the stimulation of the Na pump by stretch. The Na pump will determine ionic contents of the muscle, and these in turn may determine membrane potential and, therefore, contraction threshold. The effect of stretch in frog sartorius is relevant to the problem of stretch-induced muscle hypertrophy.

An additional project directed by Rapoport deals with the blood-brain barrier and the factors which control passage of materials through it. The project is of importance to our overall program because the blood-brain barrier regulates exchange of materials between blood and brain and therefore controls brain metabolism and is important in brain pharmacology, since some drugs are excluded by it from entering the brain. Rapoport has found a way to open the barrier by osmotically shrinking its cells. This osmotic opening is the first demonstration of reversible barrier opening that is based on morphology and simple physical-chemical laws applicable to cells in general. It will permit experimental modification of the blood-brain barrier for studying brain metabolism and perhaps for pharmacotherapy.

It is to be noted that X-ray contrast media are administered by the method of intracarotid injection to visualize the cerebrovascular tree for clinical disorders of the brain. There is a significant morbidity and mortality associated with the technique, yet the factors affecting the neurotoxicity are poorly understood. Rapoport's work shows that (a) these agents can and probably do open the blood-brain barrier because of their high osmolality, and (b) that even if they do not open the barrier, they can enter the brain and affect neurons by virtue of their lipid solubility properties. This is the first time that neurotoxicity of X-ray contrast media is considered in terms of simple physical-chemical laws of osmosis and cell membrane permeability, and it would be hoped that less toxic contrast media (with lower osmolalities and lipid solubilities) will be synthesized in the future.

II. Central Control of Movement. This general area includes projects which are under the direction of Mahlon DeLong, Edward Evarts and Fred Miles.

DeLong's studies deal with the functional role of the basal ganglia in the control of movement and posture. In carrying out studies of neuronal activity of the basal ganglia in association with movements learned by monkeys, DeLong has found preferential relation of neural activity in the putamen to slow movements. This finding may have relevance to the pathophysiology of movement disorders involving the basal ganglia in man. Considerable evidence points to a selective disturbance in slow movements in many of these

The availability of a specific antiserum to tyrosine hydroxylase should be a valuable tool for the study of such problems as the intracellular localization of tyrosine hydroxylase and the regulation of its rates of synthesis and degradation. We have already received numerous requests from investigators for samples of the antiserum. To use the metaphor used before, the antiserum is a key that undoubtedly will be used to open many doors in the future. We can anticipate, however, that because of the reduced level of personnel in the Laboratory, it will be others who will open most of these doors.

Our previous work established an important general principle about the properties of all of the pterin-dependent hydroxylase: in the presence of the naturally-occurring cofactor, tetrahydrobiopterin, substrates are better substrates (i.e., their K_m values are lower) and inhibitors are better inhibitors (i.e., their K_i values are lower) than they are in the presence of the cofactor analogue, $DMPH_4$. The main value of this generalization is that it permits us to make predictions about the properties of any single hydroxylase based on the properties of the other members of this family of enzymes.

Our recent demonstration that partially purified brain tryptophan hydroxylase is inhibited by its product, 5-hydroxytryptophan, and the fact that the inhibition is only significant in the presence of tetrahydrobiopterin, is an example of the application of this principle. All previous attempts to demonstrate this inhibition in vitro were carried out in the presence of $DMPH_4$, and were unsuccessful. On the other hand, there were strong indications that the enzyme was inhibited by its product in vivo. Our findings may have resolved this apparent dilemma since the properties of the isolated enzyme in the presence of tetrahydrobiopterin almost certainly reflect more accurately its properties in the cell than do its properties in the presence of $DMPH_4$.

Another area of research where significant progress was made last year is that of the role of the cell membrane in cellular organization and physiology. It was found that the concentration of the insulin receptor on the plasma membranes of liver cells is markedly lowered under the following conditions: 1) hyperphagia induced by hypothalamic lesions with gold thioglucose; 2) obese mice fasted in the presence of high insulin dosage; 3) glucocorticosteroid treatment; 4) ACTH treatment; 5) growth hormone treatment. Each of the above cases is associated with insulin resistance.

There are two conclusions from these studies: 1) there is a good correlation of in vivo insulin resistance and in vitro loss of insulin receptor binding, suggesting that the receptor concentration mediates these insulin resistant states; 2) the membrane receptor concentration is not a fixed entity but is variable and is under metabolic and hormonal control.

The finding that the concentration of a surface membrane receptor can be varied by hormonal and metabolic events provides a novel mode of regulating the interaction of a cell with its environment. Cells do not react in the same way to a given stimulus but can vary the concentrations of their cell surface receptors and can thus increase or decrease their sensitivity to the environmental stimulus.

It seems likely that this property is not restricted to liver cells, but extends to the way all cells, including those in the nervous system interact with their environments.

disorders. Generally speaking, the involuntary movements associated with basal ganglia dysfunction (e.g., chorea, athetosis, dystonia) are "slow" in character. Also, in the akinetic syndrome of Parkinsonism the major difficulty appears to be in the initiation of slow movements, such as rising from a chair or bed, turning, walking, etc. The initiation of simple rapid movements in Parkinsonism patients appears to be less impaired than one would expect. Kornhuber has suggested that akinesia might result from loss of the ramp-generating mechanisms of the basal ganglia, whereas rigidity, chorea, athetosis and dystonia might result from various forms of "release" of these same neural mechanisms. The present experiment, indicating that the activity of a large portion of the striatum is preferentially involved in the control of slow movements, is consistent with this view as well as the evidence for involvement of the striatum in the pathogenesis of akinesia as well as rigidity, chorea, athetosis and dystonia.

Studies on the function of the corpus striatum are of relevance to the program of the Institute since these regions of the brain appear to have important integrative as well as purely motor functions which, when disturbed as in disease, produce disturbances of movement, motivation, and affect. Current theories suggest that the site of action of L-Dopa, which abolishes symptoms in the majority of Parkinsonian patients, is upon the cells of the caudate and putamen via a dopaminergic nigro-striatal pathway. It has been suggested as well that disturbances in dopamine metabolism within corpus striatum and/or the histologically indistinguishable nucleus accumbens are involved in the pathogensis of schizophrenia, since enhancement of dopamine turnover in the brain seems to be the only distinguishing feature of the neuroleptics antipsycholic drugs (such as chlorpromazine and haloperidol). This enhancement of turnover of Dopamine within the striatum appears to result from blockade of dopamine receptors. An understanding of the normal functioning of the corpus striatum should provide a firm basis for studies on the effects of disease and pharmacologic agents on these structures.

The work of Fred Miles deals with the role of the cerebellum and vestibular nuclei in the generation of saccadic eye movements. Miles' studies of single nerve cell activity in the vestibular nuclei revealed that the activity of a large proportion of the cells in the medial and superior vestibular nuclei is very closely correlated with eye movements. Some neurones fire in relation to the position of the eyes in the orbits, others only in relation to the movement of the eyes, and yet others show both relationships; occasional units show maintained firing which is suppressed during all eye movements. Thus, each saccade is accompanied by a step, pulse, or pulse-step change in the firing of individual neurones. The precision of this coupling between single neurone behaviour and eye movements is especially impressive and the vestibular nuclei are clearly in possession of very accurate information about the oculomotor programmes. In some units the earliest changes in firing precede the eye movement by 10-20 msec, whilst in others they occur during the movement. Many neurons are strongly

directional, firing only in relation to movements of the eyes to one or other side of the orbits, whilst others--especially the pulse-type units--often fire in relation to all eye movements.

From work in other laboratories, a great deal is now known about firing patterns of oculomotor neurons in conscious monkeys, each saccade being the result of a very precisely programmed pulse-step increase in the activity of neurones supplying agonist muscles and a converse pulse-step decrease in those innervating antagonists. It is most interesting that the present study should reveal that the individual components of the saccadic programme (the transient pulse and the step change in firing) are represented in the vestibular nuclei, a finding consistent with the earlier mentioned idea that these eye-movement programmes are "compiled" in the vestibular nuclei. Since we now know that the oculomotor firing is continuously undergoing modification as a result of vestibular inputs generated by head movements, it is perhaps not unreasonable to expect the vestibular system to be intimately involved in the programming. Experiments are now under way which it is felt will help to clarify the neural mechanisms involved in computing the saccadic programme and in modifying it to compensate for movements of the head.

Evarts' work has continued to deal with the functional organization of the sensorimotor cortex in the initiation and control of movement, with recent work focused on effects of behavioral set and expectancy on activity of neurons in sensorimotor cortex of the monkey. In recent years there has been increasing debate as to the fundamental organizational pattern of the sensorimotor cortex. According to one view, activity generated by stimulation of peripheral receptors would pass in relatively unadulterated form to the sensory division of the sensorimotor cortex from whence it would flow to other cerebral structures where decisions would be made as to the behavioral responses to the input, following which information would be relayed to the motor cortex where the signals associated with voluntary movement would be generated. An alternative model has been favored by Wall, who believes that expectancy and "set" can modify input signals even prior to their arrival at the level of the sensory division of the sensorimotor cortex. Wall has written that primary sensory systems may function to control the action of convergent pathways rather than to feed into conscious decision-making centers. The availability of techniques for recording activity of neurons in intact animals has now made it possible to assess the way in which the expectancy and set modifies input-output relations in the nervous system.

In the experiment on the neuronal correlates of set, monkeys were trained to carefully maintain a certain hand position and then, shortly before the hand was perturbed, were given an "instruction" as to how they should respond to the forthcoming hand perturbation when it occurred. The "instruction" was communicated visually, as the appearance of a red light or a green light. The red light signalled to the monkey that he should pull <u>toward</u> himself when the perturbation occurred, and the green light meant that he should push <u>away</u> when the perturbation occurred. Two different sorts of perturbation were used, and there were thus four different stimulus-response

sequences. There have been two major findings. First of all, it has been found that neurons in both postcentral and precentral zones of sensorimotor cortex show changes of activity as a result of the "instruction" and prior to any direct input from hand receptors or output to hand musculature. Thus, when a light comes on instructing the animal as to whether he should push or pull later when his hand is perturbed, nerve cells of both postcentral and precentral cortex assume a discharge frequency (or "set") which is differential depending on which of the two instructions has been given. This change in sensorimotor cortex activity occurs even though there is no overt behavioral response to the instructions. Thus, there is a striking correlate between the set, attitude, or expectancy of the animal and discharge of neurons in a part of the brain which will ultimately serve to carry out the instruction. According to older views, it would have been believed that activity of neurons in sensory and motor areas would change only in association with a change in peripheral sensory input or a change in motor output. In these studies, however, changes were seen both in postcentral sensory and precentral motor divisions of the sensorimotor cortex when the animal "preset" his sensorimotor apparatus in a particular way.

A second finding concerns changes in the neuronal activity generated in sensorimotor cortex by the perturbation of the hand. As already pointed out, monkeys were trained to respond to the perturbation of the hand in one of two ways, the nature of the response depending on the prior "instruction". But in addition to two sorts of instructions, there were two sorts of perturbation of the hand, and it was found that the cortical neuronal response to the hand perturbation differed markedly depending upon the prior instruction. The difference in neuronal response as a function of instruction and "set" was present at extremely short latencies from the instant of the perturbation, latencies so short as to lead the normal activity set up by the perturbation to be referred to as a "reflex". The finding that the set, attitude, or expectancy of the subject can so profoundly modify the "reflex" response is of especial interest in view of the fact that the process was one resulting from learning.

III. Neural Correlates of Learning and Memory. This area of activity within the Laboratory of Neurophysiology includes two projects, one under the direction of Hiroaki Niki and the other under the direction of Allan Mirsky. Niki's project is concerned with studies on the neuronal activity of prefrontal cortex. He has studied the activity of prefrontal cortex nerve cells in association with behavior which is known to be dependent upon the functional integrity of this part of the brain. Tasks involving spatial memory are particularly sensitive to prefrontal damage, so it is tasks of this sort that Niki has studied. By recording from nerve cells during performance of tasks involving spatial memory, Niki has discovered neurons which are differentially related to the nature of the spatial memory that the animal holds: when an animal is required to remember whether to go right or left, there are neurons which discharge differentially according to the animal's forthcoming spatial response. It has long been recognized that the prefrontal cortex is important in higher mental processes, and it is well known that damage to the prefrontal cortex modifies

attention, emotional status, and a variety of other psychological processes without producing elementary disorders of motor or sensory behavior. Thus, it is relevant to problems of mental health to understand the way in which cells in this part of the brain are functionally organized.

A project directed by Dr. Allan Mirsky is concerned with the influence of centrally acting drugs on motor cortex nerve cell activity during attentive behavior. The overall goal of this research is to understand the central nervous system alterations occurring during impaired attentive behavior. Previous work has investigated behavioral and EEG aspects of impaired attention produced in trained monkey subjects by the administration of secobarbital and chlorpromazine. This work suggested that the mechanism of impairment produced by these two drugs differed; chlorpromazine seemed to produce primarily a phasic blocking of input process subserving arousal. Secobarbital, on the other hand, seems to suppress the functional level not only of arousal processes but of motor effector mechanisms as well. The present study was designed to focus on these effector mechanisms as they come into play during the performance of a sustained discriminated attention task. The question being investigated is whether and how neuronal activity is altered by centrally-acting drugs during attentive behavior. The methods used permit dissection of two components of the motor behavior: time to initiate the response after the "go" signal has appeared (Initiation Time) and time to execute the response (Movement Time).

Information obtained from this project is relevant to two questions of interest to the Institute: (1) the symptom of attention impairment is prominent in several diseases of largely unknown pathophysiology, i.e., schizophrenia and petit mal epilepsy. Further, it is a commonly observed characteristic of hyperkinetic children. Any information concerning alterations in central nervous system activity during impaired attention should aid in the understanding of the possible brain pathology which is associated with these clinical problems. (2) Although heroin abuse receives more attention, barbiturate abuse is probably more widespread and more dangerous from a physiological point of view. Information concerning the neural effects of barbiturates and related compounds is needed to aid in the comprehension of this problem.

IV. Neurochemical and Neuroanatomical Correlates of Behavior. This is a new area of investigation for the Laboratory of Neurophysiology, one in which no results are yet available. In this project we seek to discover structural and chemical correlates of behaviorally-related changes in nerve cell activity. One of the first problems to be undertaken in connection with this project will involve collaboration with Louis Sokoloff, who has worked out methods for determining cerebral metabolic activity in different parts of the brain by means of radioautographic studies which reveal localized uptake of deoxyglucose, the amount of this uptake relating to metabolic activity of cells. This technique is extremely promising, but has not yet been applied to studies of behavior. It is hoped that application of the technique will enable us to pinpoint regions of the brain which are selectively active in certain sorts of behavior.

Annual Report of the Section on Technical Development

National Institute of Mental Health

National Institute of Neurological Diseases and Stroke

July 1, 1972 - June 30, 1973

James S. Bryan, Chief

During the past 12 months, the Section on Technical Development (STD) continued to fulfill its traditional role of support of NIMH and NINDS research efforts. Continuing assistance was made available in shop help, special purpose instruments, instrumentation systems, and assistance in computer oriented research and digital instrumentation.

The Section continues as before to support three laboratory computers for general use, as well as the medium-size SEL 810B installation in Bldg. 10. The 810B installation is now working well, supporting as many as four simultaneous users in on-line and real-time research applications. Hardware and software support for this installation has tapered off now to a routine level of one man year for the programmer operator and one-half man year for hardware maintenance and new interface requirements. Table I gives a breakdown of laboratory computer usage by Institute. Table II shows current weekly utilization of the SEL 810B by individual sections. Table III shows a breakdown of overall activity by STD.

As usual, much research within the Section has involved collaboration with laboratories in NIMH and NINDS, and is, therefore, reported as part of the projects in the laboratories involved. Exceptions to the foregoing include our continuing efforts to develop equipment to measure motor dysfunction associated with dystonia and Parkinson's disease, and a short term project to develop a sensory aid for the blind using a binaural presentation of visual space.

The studies of Parkinsonism have progressed to routine testing of selected patients supplied by the Section on Experimental Therapeutics, Laboratory of Clinical Science, NIMH. An initial description of the testing equipment is being presented at the Rocky Mountain Bioengineering Conference in May 1973,and patient testing is going forward in an attempt to investigate an hypothesis involving a multiple feedback model for Parkinson tremor.

The short-term project to produce a visual aid for the blind began as a part-time effort on the part of a post doctoral engineer occupying a two year rotating Commissioned Corps position. This man's personal decision to leave the National Institutes of Health after one year to enter medical school caused us to accelerate the project in order to achieve some useful outcome. This accelerated effort has caused the STD project total in Table III to be substantially higher than usual for this year. The device appears to offer substantially better subjective resolution than some similar

devices such as the Bach-y-Rita tactile stimulator at the expense of increased time to present the complete "visual" field -- three to five seconds depending on content. Because of the time factor, the device seems not to be attractive for navigational guidance but may prove to be a useful vocational aid.

A total of 151 projects were completed in the last year. A large portion of these consisted of routine fabrication of various chambers, baths, electrode holders, and jigs for experimental use as well as many small electronic devices, and systems.

Major systems included:

(1) Completion of a large-animal telemetry system with one-half mile range for study of sleep patterns in free ranging wild animals - Laboratory of Clinical Psychobiology, NIMH. Last report from Africa is that the system is working well with wildebeests up to 3/4 mile range for periods up to 11 days.

(2) Expansion of the Poolesville rat colony data acquisition system - Laboratory of Brain Evolution and Behavior, NIMH.

(3) Programmed display and response system for family interaction studies - Adult Psychiatry Branch, NIMH (in process).

(4) Telemetry system for monitoring patient activity - Laboratory of Clinical Psychopharmacology, SMRC, NIMH (in process).

TABLE I

LABORATORY COMPUTER UTILIZATION

	NIMH	NINDS	NICHD	TOTAL HOURS
Classic LINC	100%	0	0	1490
MicroLINC	69%	31%	0	1931
PDP-12	32%	54%	14%	1521

TABLE II

ESTIMATED CURRENT SEL 810B UTILIZATION

	Hours per week*
Laboratory of Psychology, NIMH	
Section on Higher Thought Processes	10
Unit of Psychophysiology	30
Section on Personality	0.5
Section on Perception	5
Adult Psychiatry Branch, NIMH	
Section on Twin and Sibling Studies	0.5
Section on Perceptual and Cognitive Studies	30
Laboratory of Clinical Psychobiology, NIMH	
Section on Comparative Studies	2
System Development	8
	86*

*Timeshared terminal hours, hence more than 40 per week.

TABLE III

APPORTIONMENT OF EFFORT

ENGINEERING & FABRICATION TIME

MAJOR USERS

LABORATORY OR BRANCH	HOURS	PERCENT
Brain Evolution & Behavior, NIMH	3965	13.63
Psychology, NIMH	3873	13.31
Technical Development, NIMH/NINDS	3574	12.29
NIMH 810B Computer	3227	11.09
Clinical Psychobiology, NIMH	2625	9.02
Neurophysiology, NINDS	1810	6.22
Behavioral Biology, NICHD	1613	5.54
Adult Psychiatry, NIMH	1586	5.45
Biophysics, NINDS	1122	3.85
Office of the Director, NINDS	778	2.67
Neurophysiology, NIMH	759	2.61
Neurobiology, NIMH	478	1.64
Clinical Science, NIMH	424	1.45
General & Comparative Biochemistry, NIMH	412	1.41
Neuropathology & Neuroanatomical Sciences, NINDS	401	1.38
Experimental Neurology, NINDS	397	1.365
Molecular Biology, NINDS	386	1.327
Neurochemistry, NINDS	340	1.169
Socio-environmental Studies, NIMH	335	1.152
Cerebral Metabolism, NIMH	328	1.128
All other NINDS Labs	393	1.351
All other NIMH Labs	251	.863
NIMH (Total)	20,050	68.95
NINDS (Total)	7,414	25.52
NICHD (Total)	1,613	5.53
TOTAL*	29,077	100.0

*Not included in the foregoing totals or in the breakdown by laboratory are 1109 hours spent in routine maintenance internal to the Section, and the time of the Section Chief.

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